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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

observed that central catecholamine depletion induced an inhibition of splenic and blood lymphocyte proliferation, production and expression of splenic cytokines IL-2 and IFN-γ 7 days after 6-hydroxydopamine (6-OHDA) i.c.v. injection in rats. In addition, central treatment with 6-OHDA reduced the percentage of spleen and peripheral blood NKCC, and T-cytotoxic cells in peripheral blood. Moreover, Oberbeck et al. (2004), who investigated the effect of epinephrine and/or beta-adrenergic blockade on cellular immune functions during systemic inflammation, indicated that adrenergic mechanisms modulate cellular immune functions and survival during sepsis, with these effects being mediated via alpha- and beta-adrenergic pathways.

2.1.2. The dopaminergic pathway: dopamine (DA)

A correlation between the brain and peripheral dopamine (DA), a catecholamine neurotransmitter, and the immune response has been recently suggested (Basu and Dasgupta, 2000; Levite et al., 2001; McKenna et al., 2002; Carr et al., 2003). Previously, lateralized depression of spleen NKCC in mice was found after destroying of the dopaminergic terminals in the mesolimbic nucleus accumbens (Deleplanque et al., 1994). Furthermore, an enhanced proliferative responses and decreased numbers of IFNγ-producing cells in the spleen in mice after in vivo DA administration, has been recently demonstrated (Carr et al., 2003). On the other hand, elevated physiological concentrations of DA were found to inhibit significantly the proliferation and cytotoxicity of $CD4^+$ and $CD8^+$ cells in vitro (Saha et al., 2001). The authors emphasized that the underlying mechanism was D1 class of dopamine-receptor-mediated stimulation of intracellular cAMP. Moreover, according to Teunis et al. (2004) splenic NK cell activity of hyperdopaminergic rats is significantly lower than NK cell activity and percentages of NK cells of their hypodopaminergic counterparts. Torres et al. (2005) revealed that NE and DA increased lymphocyte activation accompanied by augmented Th1 and Th2 type cytokine production while the action of NE together with dexamethasone resulted in immunosuppression.

2.1.3. The peptidergic pathway: neuropeptides

In addition to the substantial body of evidence for noradrenergic neurotransmission with cells of the immune system, there is also more circumstantial evidence for a neuropeptidergic link with cells of the immune system (Felten et al., 1985; Bellinger et al., 1990), several neuropeptides are also located in nerve terminals innervating primary and secondary lymphoid organs (e.g., vasoactive intestinal peptide (VIP), cholecystokinin (CCK), substance P (SP), and neuropeptide Y (NPY).

Recently, the direct effect of such neuropeptides and neurotransmitters as calcitonin-gene-related-peptide (CGRP), NPY, somatostatin (SOM), SP, DA, and glutamate on human and mouse T cells was observed (Levite, 1998, 2000; Levite and Chowers, 2001; Ganor et al., 2003). According to the authors, normal, cancer, and autoimmune human T-cells, alike neurons, express high levels of ion-channel glutamate receptors of the AMPA subtype-3 (GluR3), identical to the brain GluR3, and human T-cells express on their outer membranes functional dopamine receptors of the D3 and D2 subtypes (Levite et al., 2001). Signaling through these receptors has been shown to modulate T cell functions such as proliferation, integrin-mediated adhesion and cytokine secretion, being thus potentially very relevant in normal and pathophysiological brain–immune system interactions (Levite, 2000; Levite and Hart, 2002). For instance, it was suggested (Levite, 2002) that some epilepsies can be autoimmune-mediated since distinct subpopulations of epilepsy patients harbor elevated levels of antibodies to either the GluR3B peptide of AMPA receptors, or glutamate/NMDAR2A receptor or dsDNA. In addition, anti-GluR3 and anti-dsDNA antibodies are present on boht sides of the blood–brain barrier and anti-GluR3 antibodies can activate homomeric and heteromeric GluR3 and elicit ion currents, acting alike glutamate agonists and kill neurons (Levite et al., 1999; Ganor et al., 2005).

In activated macrophages, VIP and pituitary adenylate cyclase activating polypeptide (PACAP) inhibit the expression at both mRNA and protein level of pro-inflammatory cytokines and chemokines, through effects on de novo expression or nuclear translocation of a number of transcription factors, i.e., NFkB, CREB, c-Jun, JunB, and IRF-1 (Ganea et al., 2003; Ganea and Delgado, 2003). In addition, VIP and PACAP affect the differentiation of $CD4^+$ T cells directly and indirectly through antigen-presenting cells and promote the proliferation and/or survival of the Th2 effectors (Delgado et al., 2004a,b). Among the other neuropeptides, several functions of the cellular immune system have been shown to be regulated by NPY (De la Fuente et al., 1993; Levite, 2000; Bedoui et al., 2003). According to Puerto et al. (2005) the effects of NPY and NE, separately or jointly on the lymphoproliferation, NK activity and IL-2 and TNF-α release were different depending on the age of the mice. SP, neurotransmitter facilitates lymphocyte migration to the inflammatory site, enhances lymphoproliferative response to mitogenic stimulation and lymphocyte production of IgA, and promotes phagocytosis and chemotaxis (Pascual et al., 1991; Feistritzer et al., 2003). Recently, Jing et al. (2004) described the inhibitory effect of prostaglandin E(2) (PGE(2)) on the expression and release of the inflammatory chemokines CCL3 and CCL4 from activated dendritic cells and Vassiliou et al. (2004) proposed a novel function for PGE(2) as a bone marrow-derived dendritic cell survival factor.

2.1.4. The cholinergic pathway: acetylcholine (Ach)

Recent evidence shows an important role of the parasympathetic nervous system in the bidirectional communication between the brain and the immune system, underlying the ability of the brain to monitor immune status and control inflammation through the cholinergic pathway (Kawashima and Fujii, 2003; Pavlov and Tracey,

2004; Czura and Tracey, 2005). Radioligand binding and gene expression studies have detected both muscarinic and nicotinic acetylcholine (Ach) receptors on both human and rodent T lymphocytes (Kawashima and Fujii, 2000) and macrophages (Tracey, 2002). Recent findings that Ach-secreting neurons of the parasympathetic nervous system suppress acute inflammation are now coined as the inflammatory reflex (Tracey, 2002). Termed the 'cholinergic anti-inflammatory pathway', described as a novel function of the efferent vagus nerve (Czura et al., 2003; Pavlov et al., 2003) plays a critical role in controlling the inflammatory response through interaction with peripheral alpha7 subunit-containing nicotinic Ach receptors expressed on macrophages, leading to cellular deactivation and inhibition of cytokine release. Moreover, Zimring et al. (2005) revealed that development of $CD8^+$ cytolytic T lymphocytes is inhibited by acetylcholinesterase, which suggests that Ach is required for generation of cytolytic lymphocytes. According to Saeed et al. (2005), both vagus nerve stimulation and cholinergic agonists significantly blocked endothelial cell activation and leukocyte recruitment during inflammation.

2.1.5. The hypothalamic–pituitary–adrenal (HPA) axis

In addition to SNS activity, the immune system is influenced by neuroendocrine outflow primarily from the HPA. Although there are direct immunomodulatory effects of CRH and ACTH, their major in vivo effects are exerted through interactions with other hormones and immune system products (Berczi, 1986; Heijnen et al., 1991b; Labeur et al., 1995). Urocortin, a neuropeptide related to CRH, is an important neuropeptide involved in the brain control of peripheral immune functions (Okamoto et al., 1998; Gysling et al., 2004). According to Okamoto et al. (1998) in stress-induced immunosuppression the suppressive effect of urocortin is mediated by the SNS. Endogenous opioid peptides, especially the endorphins and enkephalins, directly influence antigen specific and non-specific in vitro responses, the direction and magnitude of the effects being determined by several factors including the nature and quality of the peptides, their binding sites, and the timing of the administration of antigenic stimulation in relation to dose and route (Plotnikoff et al., 1985; Heijnen et al., 1991a; Adler et al., 1993). Although there are direct immunomodulatory effects exerted through interactions with other hormones and immune system products (Berczi, 1986). Lang et al. (2003) have shown that the neurotransmitters: endorphin, histamine and SP increase NKCC, while NE inhibits cytotoxicity. According to the author, SP reduces migratory activity, while NE increases NK cell and cytotoxic T cell migration. In addition, in vitro treatment of β-endorphin on NK cells increased the levels of perforin, granzyme B and IFN-γ and their mRNA transcripts, whereas ethanol pre-treatment prevented β-endorphin effects on cytolytic factors in these cells (Dokur et al., 2005).

GH and PRL are known to stimulate immune responses (Kelley, 1989; Dorshkind and Horseman, 2000; Esquifino et al., 2004; Carreno et al., 2005). In rodents, deficiencies of GH are associated with abnormal cellularity of the bone marrow and thymus, together with diminished antibody production, T-cell function, and NK-cell activity. These effects are, to a large extent, overcome by the administration of exogenous GH (Kelley, 1989). The original idea that GH interacts with glucocorticoids was more recently confirmed by Dobashi et al. (2001). The authors showed that human GH and its downstream mediator, insulin-like growth factor-I (IGF-I), significantly attenuate dexamethasone-induced inhibition of human T cell proliferation induced by immobilized anti-CD3 and CD28 monoclonal antibodies. Inhibition of pituitary PRL secretion suppresses antibody and cell mediated immune functions and increases susceptibility to infections such as *Listeria monocytogenes*. These defects in immune function can be reversed by exogenous treatment with PRL or DA antagonists given to stimulate endogenous release of prolactin. PRL released in response to stressful experiences counters many of the immunosuppressive effects of corticosteroids.

The HPA axis is activated during many bacterial and viral infections, resulting in an increase in circulating hormone levels, including corticosteroids. Glucocorticoids are the main effector end point of the neuroendocrine system and, through the glucocorticoid receptor (GR), have multiple effects on immune cells and molecules (Webster et al., 2002). The suppressive effects of glucocorticoids on inflammatory cell function have been the subject of numerous reviews (Munck and Guyre, 1991; DeRijk and Sternberg, 1994; Goldstein et al., 1994; Konstan, 1996; Miller and Levy, 1997). In cells of the immune system, glucocorticoids particularly affect proliferation and survival or apoptosis of T cells (Wyllie, 1980; Ucker, 1987). Some bacteria and viral infections have been shown to affect the GR directly (Webster and Sternberg, 2004). Moreover, bacterial toxin, anthrax lethal toxin, at very low concentrations represses glucocorticoid and progesterone receptor activity (Webster et al., 2003). According to the authors, simultaneous loss of GR and other nuclear receptor activities could render an animal more susceptible to lethal or toxic effects of anthrax infection by removing the normally protective anti-inflammatory effects of these hormones. On the other hand, in physiological doses, glucocorticoids are essential for normal immune function and they are immunomodulatory rather than solely immunosuppressive, causing a shift in patterns of cytokine production from a TH1- to TH2-type pattern (Sternberg, 2001; Eskandari and Sternberg, 2002). In some circumstances, corticosteroids can be immunoenhancing (Jeffries, 1991). Currently, Truckenmiller et al. (2005) have demonstrated that stress-induced suppression of the host defences against viral decreases may be due to corticosterone impairments of MHC class I antigen presentation by dendritic cells via reduction of antigenic peptide generation.

Moreover, corticosteroid sensitivity may be a factor in the pathogenesis and could be used for prognosis of multiple sclerosis (DeRijk et al., 2004). Estrogen also plays an important role in immune modulation (Sapino et al., 2003), and contributes to the approximately 2- to 10-fold higher incidence of autoimmune/inflammatory diseases seen in females of all mammalian species (Sternberg, 2001). Furthermore, steroid hormones such as testosterone and estradiol, exerted a regulatory influence on both cytotoxicity and migration of NK cells (Lang et al., 2003).

2.2. Brain areas involved in immunomodulation

Some investigators have taken a neuroanatomic approach to evaluate the role of the CNS in modulation of immune reactivity (Fig. 1A,B). Support for a concept of neural–immune interactions was found in reports which indicated that damage to the CNS by electrolytic lesions especially in the hypothalamus and limbic system induce a variety of immune alterations (Carlson and Felten, 1989; Hass and Schauenstein, 1997). Studies utilizing CNS lesions or stimulation suggest that specific regions of the brain may modulate immune activity. However, the usefulness of stereotaxic ablation as an experimental approach is limited because of the inability to destroy specific nuclei without damaging passing tracts from other regions. Furthermore, electrical stimulation has been shown to affect not only the cell bodies of the neurons, but also axons passing through the vicinity of the electrode tip. However, these studies do suggest areas and pathways throughout the CNS that may be important in influencing outflow to the immune system (Tables 1 and 2).

The neurohumoral activities of the hypothalamus, its anatomical and functional links with cortical and subcortical

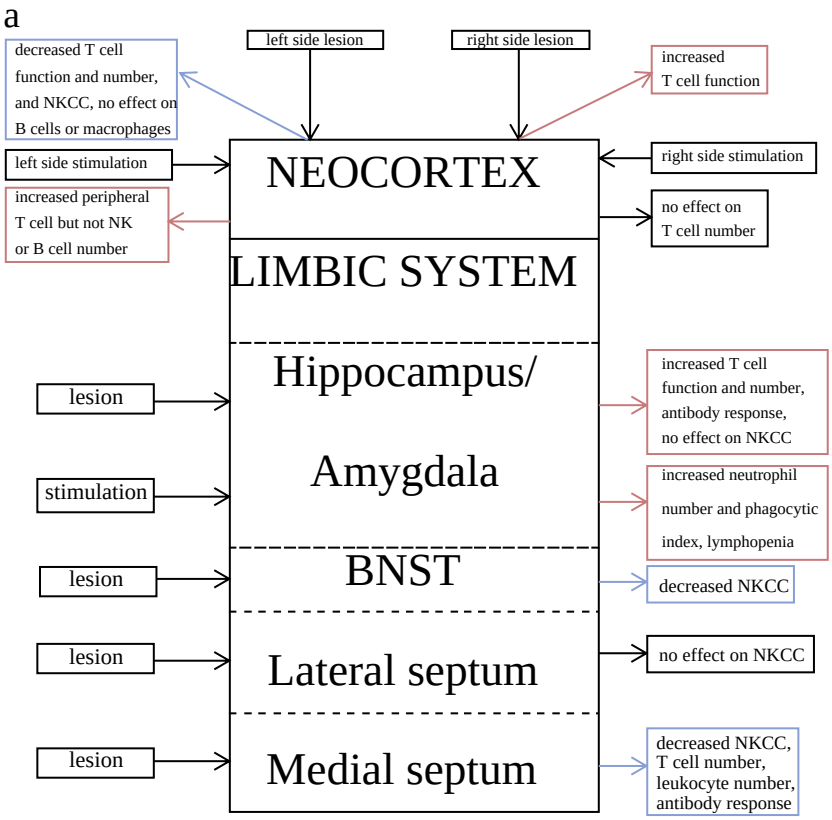

Fig. 1. The scheme of the results of stereotaxic method used to study the location of brain areas involved in immunoregulation. Neocortical influences on immune response are lateralized with the two hemispheres of the brain modulating one another (A). Moreover, there is a direct neocortical influence on thymic production mediated by the sympathetic nervous system. The parts of the limbic system are differently involved in the immune function modulation: lesions of the hippocampus/amygdala complex had generally resulted in enhancement of several immune parameters while lesions of either septum or bed nucleus of stria terminalis (BNST) region decreased immune functions. Lesions of the preoptic/anterior (AH) parts of the hypothalamus usually evoked decreased immune function which suggests their immunoenhancing effect (B). The paraventricular nucleus of the hypothalamus (PVN) represents an integral part of the neuro-endocrine circuit modulating the immune function and is proposed as an integrative center for immunomodulation. Both lesion and stimulation of the ventral nucleus of the hypothalamus (VMH) had the same immunosuppressive effect which was connected with behavioral outcome of VMH stimulation (behavioral inactivation or aversive response). The brain structures related to positive reinforcement (reward) such as the lateral hypothalamus (LH) and ventral tegmental area (VTA) enhanced immune function and behavioral outcome of LH/VTA stimulation (eating or locomotor response) may influence this immunoenhancing effect. There are opposite immune effects of the stimulation of the dorsal and ventral part of the periaqueductal gray matter (PAG) or lesion of the vestibulocerebellum (vestibulo) or fastigial nuclei of cerebellum (fastigial). Explanations: red arrow and box: immunoenhancing effect of lesion or stimulation; blue arrow and box: immunosuppressive effect of lesion or stimulation; black arrow and box: no effect or no definite effect of lesion or stimulation.

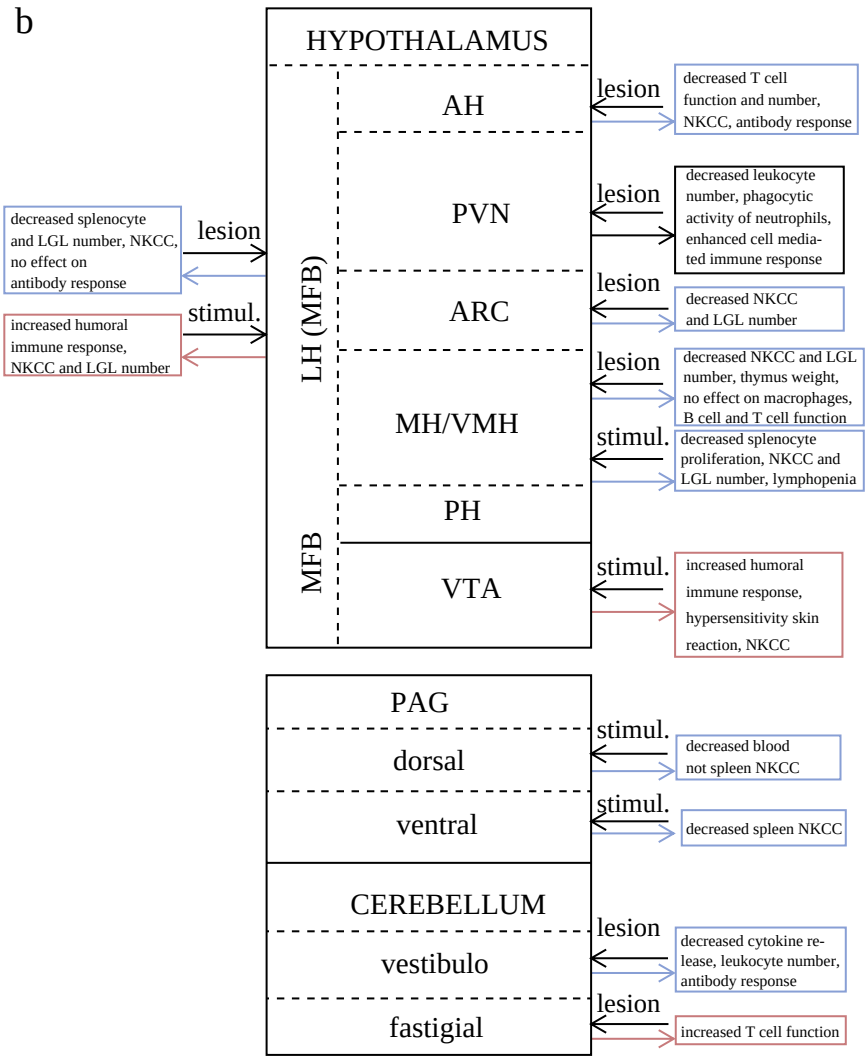

Fig. 1 (*continued*).

brain structures, and its regulatory control over many physiological functions made this structure of particular interest for immunological investigations.

2.2.1. The preoptic/anterior hypothalamus (AH)

In the previous studies on the effects of discrete sites of the hypothalamus on immune functions, the most remarkable and consistent effects were observed only in those focusing on the medial part of the preoptic and anterior hypothalamus (Isakovic and Jankovic, 1973; Cross et al., 1980, 1982; Keller et al., 1980; Roszman et al., 1982; Cross et al., 1984; Hara, 1986; Katayama et al., 1987; Katafuchi et al., 1993; Mori et al., 1993; Take et al., 1995). As demonstrated over 30 years ago (Isakovic and Jankovic, 1973) significant involution of the thymus occurred in all rats 32 days after electrolytic damage of the anterior hypothalamus, reticular formation, thalamus, superior colliculus, caudate nucleus and amygdaloid complex. The cellular architecture of the spleen and lymph nodes was affected only in hypothalamus-lesioned animals. The principal findings were a decrease in the number of lymphocytes and plasma cells and the absence of germinal centers. Decreased antibody production (Tyrey and Nalbandov, 1972), the ability to prevent or control tumor growth (Sobue et al., 1981), and the development of a lethal anaphylactic response (Stein et al., 1981) was also observed following lesions of the anterior part of the hypothalamus. Cross et al. (1980, 1982) and Keller et al. (1980) have shown that destructive lesions of the AH area result in markedly diminished in vitro cell-mediated immune responsiveness and thymic involution which was unrelated to corticosteroid production release. The same group (Roszman et al., 1982) also noted that animals with electrolytic lesions of this area have impaired mitogen-induced lymphocyte blastogenesis which is restored by removal of the population of spleen cells with macrophage-like properties, suggesting CNS regulation of this splenic suppressor cell population. In a subsequent report, Cross et al. (1984) have shown that rats with AH lesions have a decrease in NK activity 4 and 7 days after lesioning, with a return to normal

Table 1
The summary of the effect of the lesion (L) or stimulation (S) of the discrete brain areas on the immune response: the preoptic/anterior hypothalamus (AH), arcuate nucleus (ARC), hypothalamic paraventricular nucleus (PVN), medial hypothalamus (MH), ventromedial hypothalamus (VMH), vestibulocerebellum (VEST), cerebellar fastigial nuclei (FAST), ventral periaqueductal gray (VPAG), and dorsal periaqueductal gray (DPAG)

Brain area	L/S (animal)	Immune response	Reference
AH	L (rat)	Thymus involution, reduced spleen white pulp and plasma cells, depletion of lymphocytes in the lymph nodes	Isakovic and Jankovic, 1973
AH	L (rat)	Reduced antibody production	Tyrey and Nalbandov, 1972
AH	L (rat)	Decreased ability to prevent or control tumor growth	Sobue et al., 1981
AH	L (rat)	Decreased lethal anaphylactic response	Stein et al., 1981
AH	L (rat)	Independent of corticosterone thymic involution	Cross et al., 1980, 1982
AH	L (guinea pig)	Inhibited lymphocyte proliferation	Keller et al., 1980
	L (rat)		Roszman et al., 1982
AH	L (rat)	Reduced NKCC	Cross et al., 1984
AH	L (rat)	Suppressed lymphocyte blastogenesis and accelerated tumor growth	Hara, 1986
AH	L (mouse)	Reduced T lymphocyte number	Katayama et al., 1987
	L (rat)		Mori et al., 1993
	L (rat)		Utsuyama et al., 1997
AH	S (cat)	Granulocytosis, lymphopenia, increased surface expression of CD62L on $CD4^+$ and $CD8^+$ cells	Mori et al., 2000
ARC	L (mouse)	Decreased spleen NKCC and LGL number	Belluardo et al., 1990b
PVN	L (rat)	Attenuated stress-induced proliferative response in blood, decreased spleen proliferative response	Pezzone et al., 1994
PVN	L or isolation (rat)	Decreased blood leukocyte number and phagocytic activity of neutrophils, enhanced cell-mediated immune function	Hefco et al., 1993, 2004
PVN	c-*fos* study (rat)	IL-1β-induced Fos expression in the magnocellular neurons	Yang et al., 1997
MH	L (mouse)	Reduced spleen NKCC and LGL number, no effect on macrophage, B- and T lymphocyte functions	Forni et al., 1983; Belluardo et al., 1987, 1990a
MH	L (rat)	Decrease thymus weight and its cellularity, no effect on PFC, antibody titre, leukocyte migration	Devi and Namasivayam, 1996
VMH	Acute S (rat)	Reduced proliferation of splenocytes	Okamoto et al., 1996
VMH	S (cat)	Granulocytosis, lymphopenia including $CD4^+$ and $CD8^+$ cells	Kaname et al., 2002
VMH	Chronic S (rat)	Behaviorally dependent reduced blood and spleen NKCC and LGL number	Wrona and Trojniar, 2005
VEST	L (rat)	Decrease of bone marrow and thymus cytokines, blood leukocyte number, neutrophil myeloperoxidase response and antibody titer to SRBC	Ghoshal et al., 1998
FAST	L (rat)	Enhancement of Con A-induced lymphocyte proliferation	Peng et al., 2005
VPAG	S (rat)	Morphine-mediated, naltrexone-sensitive suppression of splenic NKCC	Weber and Pert, 1989, 1990
DPAG	S (rat)	Decrease in blood but not splenic NKCC, no effect on mitogen responses	Demetrikopoulos et al., 1994

activity by day 14. In addition to the results of previous studies, Hara (1986) has demonstrated suppressed lymphocyte blastogenesis and accelerated subcutaneous tumor growth after bilateral AH lesion. Moreover, Belluardo et al. (1990a) have found that destruction of the hypothalamic arcuate nucleus with the neurotoxin monosodium glutamate in newborn mice resulted in depressed NKCC and LGL number activity and in the disappearance of its age-dependent pattern. In same cases, hypophysectomy (Cross et al., 1982; Tyrey and Nalbandov, 1972) or adrenalectomy (Tyrey and Nalbandov, 1972) reversed the effects of AH lesions, suggesting that at least some of the effects of these lesions on the immune system are mediated via the pituitary hormones or peptides or other neuroendocrine routes. Other studies have shown a decreased CD4/CD8 ratio of peripheral blood and spleen lymphocytes as well as their proliferative response to PHA after making AH lesions which indicate the enhancing effect of anterior hypothalamus on T cell functions (Katayama et al., 1987; Mori et al., 1993; Utsuyama et al., 1997). More recently, Mori et al. (2000) reported that electrical stimulation of AH induced changes in the leukocyte distribution (granulocytosis and lymphopenia) and surface expression of adhesion molecules (increased surface expression of CD62L on $CD4^+$ and $CD8^+$ cells) in the cats.

These results suggested that the intact preoptic and anterior hypothalamus may be important for normal humoral and cell-mediated immune functions and these structures enhance immune response via endocrine and/or sympathetic activity systems.

2.2.2. The hypothalamic paraventricular nucleus (PVN)

The paraventricular nucleus (PVN) of the hypothalamus is involved in the integration and regulation of a variety of neuroendocrine (Swanson et al., 1983; Kiss et al., 1991; Hosoya et al., 1995) and autonomic, predominantly

Table 2
The summary of the effect of the lesion (L) or stimulation (S) of the discrete brain areas on the immune response: the lateral hypothalamic (LH), ventral tegmental area (VTA), amygdaloid complex (AM), hippocampus (HIP), septum (SEP), bed nucleus of stria terminalis (BNST), dopaminergic mesolimbic pathways (MESO) and cortex

Brain area	L/S (animal)	Immune response	Reference
LH	L (rat)	Reduced antiviral activity, no effect on antibody response to bacterial antigen and SRBC	Fessel and Forsyth, 1963
LH	L (rat)	Biphasic (depression, enhancement, further depression) change in blood NKCC, decreased LGL number at the late not early postlesion period	Wrona et al., 1994
LH	L (rat)	Independent of LGL number decrease in spleen NKCC	Iimori et al., 1998
LH	L (rat)	Apoptosis-induced decrease of the spleen weights and splenocyte number	Tsuboi et al., 2001
LH	L (rat)	Motility level-dependent decrease of NKCC and LGL number, no effect of motility level or lesion on PWM proliferation	Wrona et al., 2003
LH	Self-S (rat)	Enhanced PFC response and anti-SRBC antibody titer	Sakic and Vlajkovic, 1990
LH	Self-S (rat)	Increased humoral immune response, no effect on delayed hypersensitivity skin reactions to BSA and inflammatory foot swelling	Vlajkoviæ et al., 1993
VTA	Self-S (rat)	Higher than in LH increase of humoral response, increased hypersensitivity skin reaction to BSA, no effect on inflammatory foot swelling	Vlajkoviæ et al., 1993
LH	Acute S (rat)	Independent of LGL number increase in spleen NKCC	Iimori et al., 1998
LH	Self-S (rat)	Increase in spleen NKCC	Wenner et al., 2000
LH	Chronic S (rat)	Dependent on behavioral outcome of stimulation increase in blood and spleen NKCC and LGL number	Wrona and Trojniar, 2003
VTA	Chronic S (rat)	Independent of LGL number or endocrine release increase in spleen but not blood NKCC	Wrona et al., 2004
LH	Electroacupuncture (rat)	Increase in NKCC	Choi et al., 2002; Hahm et al., 2004
AM, HIP	L (rat)	Increased thymocyte and splenocyte number, enhanced Con A proliferation	Brooks et al., 1982; Cross et al., 1982; Pan and Long, 1993
HIP	L (rat)	Increased antibody response to ovalbumin	Nance et al., 1987
AM	L (rat)	No effect on NKCC	Grijalva et al., 1990; Jurkowski et al., 2001
HIP	L (mouse)	$CD4^+$ T cells and B cells prevent lesion-induced neurodegenerative process	Chen et al., 2004
HIP	S (rat)	Increased neutrophils number and phagocytic index, decreased lymphocyte number	Devi et al., 1993
SEP	L (rat)	Reduced antibody responses to ovalbumin	Nance et al., 1987
SEP	L (rat)	25-day inhibition of Con A, PHA, and PWM proliferation of T lymphocytes	Labeur et al., 1991
SEP	L (rat)	Increase in NKCC in females only	Wetmore et al., 1994
SEP	L (rat)	Decrease in leukocyte number	Zach et al., 1999
SEP, BNST	L (rat)	Suppression of blood NKCC	Jurkowski et al., 2001
MESO	L (mouse)	Decreased splenic NKCC and no effect on T lymphocyte mitogenesis in left-lesioned group	Deleplanque et al., 1994
MESO	L (rat)	Decreased immune response in SRBC immunized group	Devoino et al., 1997
cortex	L (mouse)	Decreased NKCC and T-cell number and function and no effect on B lymphocytes and macrophages following left hemisphere lesion, enhancement of T-cell function following right hemisphere lesion	Renoux et al., 1983; Neveu et al., 1986; Renoux et al., 1987; Neveu et al., 1989; Neveu, 1992
cortex	S (rat)	Increase in circulation levels of T cells but not NK or B cells following left-side stimulation, no effect on T cells levels following right-side stimulation	Moshel et al., 2005

sympathetic, functions (Yoshimatsu et al., 1984; Hosoya et al., 1995) which have been shown to influence the immune function.

According to Pezzone et al. (1994) in PVN-lesioned rats, the shock-induced suppression of lymphocyte proliferation in the peripheral blood and the elevation of plasma corticosterone were significantly attenuated, while lymphocyte proliferation in the spleen was suppressed below the level of the sham-treated animals. The authors suggest that PVN may play a direct role in the alteration of lymphocyte function during stress, and an intact PVN buffers the effect of the stress on the responsiveness of spleen lymphocytes to non-specific mitogens. The reports of Hefco et al. (1993, 2004) have provided the evidence that in rats mechanical lesion or isolation of the PVN selectively reduces circulating white blood cells and the primary immune response measured as phagocytic function of circulating neutrophils, while it enhances the cell-mediated immune function.

According to the authors, PVN enhances cell-mediated immune functions by altering both the peripheral sympathetic tone and thyroid hormone secretion and they suggest that PVN represents an integral part of the neuroendocrine circuit modulating the immune function of the organism. Furthermore, using the c-*fos* technique to detect the activated neurons, Yang et al. (1997) demonstrated that intraventricular injection of IL-1β induced Fos expression in the magnocellular neurons of the PVN. The authors proposed the PVN as an integrative center for immunomodulation via three channels, i.e., the CRH and oxytocin neuroendocrinological and the PVN-spinal cord sympathetic neural channels.

2.2.3. The medial hypothalamus (MH)

Until the present, a few reports have been published concerning the possible involvement of the medial part of the hypothalamus (MH) in the modulation of the immune response (Forni et al., 1983; Belluardo et al., 1987; Katafuchi et al., 1994; Okamoto et al., 1996; Belluardo et al., 1990b; Kaname et al., 2002; Wrona and Trojniar, 2005). Studies of Forni et al. (1983) and Belluardo et al. (1987, 1990b) revealed that electrothermocoagulation of the individual nuclei of the MH in the C57BL/6 mouse leads to a significant reduction in the NKCC and LGL number compared with intact or sham-operated controls. Macrophage, B- and T-lymphocyte functions, however were not significantly affected (Forni et al., 1983). On the other hand, according to Devi and Namasivayam (1996), in immunized rats with the VMH lesions, with the exception of the decrease in thymus weight and its cellularity, other parameters such as PFC, antibody titre, leukocyte migration inhibition index did not differ from the controls. The involvement of hypothalamic tubero-mammilary areas whose localization was ascertained through stereotactical methods, in maintenance of basal phagocytosis and of the primary and secondary specific immune response following lesions studies in dogs was recently reviewed by Baciu et al. (2003).

In the stimulation paradigm studies, the most focused MH area was the ventromedial hypothalamic nucleus (VMH) which is known to regulate both the sympathetic and vagal nerve functions indirectly via many projections, and its electrical stimulations to affect the HPA axis directly and indirectly (Oomura, 1983; Grijalva and Novin, 1990). According to Okamoto et al. (1996) acute (30 min) electrical stimulation of the VMH caused a remarkable decrease in the mitogenic response of splenic lymphocytes to Con A in rats. The authors emphasized that this immunosuppressive effect is mediated through the activation of the sympathetic nerves via the β-adrenergic pathway. More recently, Kaname et al. (2002) reported that VMH electrical stimulation, which elicits threat behaviors, induced granulocytosis and lymphopenia, including $CD4^+$ and $CD8^+$ cells, the decrease in the surface expression of CD62L on $CD4^+$ and $CD8^+$ cells or granulocytes which were concomitant with elevations of plasma cortisol, epinephrine and norepinephrine levels in the peripheral blood in cats. Currently, Wrona and Trojniar (2005) have reported that chronic (21 day) electrical VMH stimulation decreases both peripheral blood and spleen NKCC and LGL number in rats. According to the authors, this immunosuppression was connected with behavioral outcome of VMH stimulation (aversive response vs. behavioral inactivation) rather than endocrine changes.

It may be worth pointing out that lesions and stimulation (acute and chronic) of VMH had the same immunosuppressive effect, while in other structures such effects are usually antagonistic.

2.2.4. The lateral hypothalamus (LH) and ventral tegmental area (VTA)—the "brain reward system"

Several lines of recent evidence indicate that the positive or negative emotional state of the man or animal may influence immunological parameters via the limbic–hypothalamic circuits, which represents the neurophysiological background of emotionality. The lateral hypothalamus and ventral tegmental area were identified as a very effective locus for brain stimulation reward (positive reinforcement) and they are involved in food, water and sex appetitive reactions (e.g., Olds, 1956; Valenstein, 1969, 1976; Hoebel, 1971).

The role of the LH in immunity has been investigated since 1963, when Fessel and Forsyth demonstrated a doubling of γ-globulin levels by electrical stimulation of the LH in rats. Baciu and Ivanow (1984) performed lesion experiments on various parts of the rat hypothalmus. According to the authors, lesions of LH did not alter immune response following immunization with a bacterial antigen (*Salmonell enteritidis*) and a cellular antigen (SRBC). On the other hand, primary and secondary immune responses were reduced when rats were challenged with a viral antigen (*Myxovirus influenza A*). Furthermore, Guschin et al. (1989) have revealed that LH lesions cause a significant decrease of the weight of spleen primaral follicules which contain IgM^+ IgD^+-bearing B-lymphocytes displaying the characteristics of a circulating pool of B-lymphocytes in rats. In the LH-self stimulating rats, an enhanced plaque-forming cells (PFC) response and increased anti-SRBC antibody titer were observed by Sakic and Vlajkovic (1990). In a subsequent report, the same group (Vlajkoviæ et al., 1993) compared the results of LH and VTA stimulation on the immune responses. Using a self-stimulation paradigm they found that VTA potentiated delayed hypersensitivity skin reactions to BSA, while LH failed to change delayed type reactions. Inflammatory foot swelling, induced by cell-mediated immune reaction to Mycobacterium tuberculosis, was not affected by stimulation of either structure. On the other hand, VTA and LH self-stimulation significantly increased humoral immune responses. The immunoenhancement was higher in the VTA—than in the LH-self-stimulating animals. According to the authors, the effects of self-stimulation on the immune

responses was dependent on the localization of the electrode tip in the brain reward system (LH vs. VTA), the type of immune reaction (humoral vs. cellular), the antigen used for immunization (SRBC vs. BSA), and the timing of the stimulation procedure with respect to the immunization (before vs. after). Wrona et al. (1994) have found that in LH-lesioned rats, peripheral blood NKCC shifts from depression through enhancement to further depression on the 2nd, 5th and 21st postlesion day, respectively. According to the authors, the decrease in NKCC at the late rather than the early postlesion period was correlated with the decrease in LGL number. More recently, the same authors (Wrona et al., 2003) have shown that individual differences measured as spontaneous locomotor activity (high vs. low responders) influence the level of peripheral blood NKCC at the baseline and following LH lesions in the rats. On the other hand, the proliferative lymphocyte response to PWM and plasma corticosterone was not affected either by the motility level or by the LH lesion. According to Tsuboi et al. (2001) in the LH-lesioned rats, spleen weights and the number of splenocytes decreased significantly within 24 h. The authors suggest that LH may play a role in immunoregulation by affecting lymphocytes in the spleen through apoptosis and may be relevant to the pathway of stress-induced apoptosis. Further studies of Wenner et al. (1996) and Iimori et al. (1998) revealed that splenic NKCC respectively increased and decreased following acute (30 min) electrical stimulation or ablation of the LH without simultaneous changes in the NK cell number. The authors suggested that following acute LH stimulation the increase in target cell destruction was due to the enhanced intrinsic activity of a single NK cell. Moreover, increase in spleen NKCC was observed after uncontrollable LH stimulation in conscious rats by the same group (Wenner et al., 2000) and in both blood and spleen NKCC following chronic (21 day) electrical stimulation (Wrona and Trojniar, 2003) in conscious, freely behaving rats.

Furthermore, recently Wrona and Trojniar (2003) and Wrona et al. (2004) have found that chronic but not acute electrical stimulation of both reward-related areas (VTA and LH) caused an increase in NKCC in conscious, freely behaving rats. Chronic LH stimulation resulted in increased blood and spleen NKCC and LGL number while VTA stimulation increased spleen but not blood NKCC without any simultaneous effect on the number of LGL and plasma level of prolactin, growth hormone, corticosterone, and testosterone. According to the authors, the effect pronounced by VTA is weaker than that of LH, possibly due to some additional connections of LH with the hormonal and/or autonomic control systems. Moreover, the authors suggest that behavioral outcome of LH/VTA stimulation (eating vs. locomotion) may influence its immunoenhancing effect.

In parallel with stereotaxic methods used to study the location of brain areas involved in immunoregulation, the different distribution of cytokine immunopositive cells in the brains of rats immunized via both intraperitoneal and subcutaneous injections were studied by Gao et al. (2000). The authors have observed that neurons of the LH and amygdaloid nuclear complex in hypothalamus played a key role in neuroimmunomodulation and participated in the neuroimmunoregulation at an early stage of the immune response. Moreover, Choi et al. (2002) have shown that LH is closely related to increase of NK cell activity induced by electroacupuncture in rats and Hahm et al. (2004) have suggested that electroacupuncture delivered through LH for 30 min enhances or restores the splenic NK cell activity suppressed by an anterior hypothalamic area lesions in rats.

These findings emphasized that brain structures related to positive reinforcement (reward) have beneficial effect on immune response, including antiviral and antitumor cytotoxic activity of lymphocytes.

2.2.5. The limbic structures

Despite the predominant hypothalamic focus on CNS involvement in shaping the immune system, it has been proposed that the limbic structures and neocortex also influence the immune response (Carlson and Felten, 1989; Hass and Schauenstein, 1997). Lesions within the limbic system have generally resulted in enhancement of several immune parameters. Brooks et al. (1982), Cross et al. (1982), and Pan and Long (1993) have shown that lesions in the amygdaloid complex and the hippocampus in rats led to increased numbers of thymocytes and spleen cells and enhanced their proliferative responses to Con A. Devi et al. (1993) have shown that a 4-day electrical stimulation of the hippocampus increased the number of neutrophils and phagocytic index while also decreasing the number of lymphocytes and plasma corticosterone level in rats. The alterations in cell number and mitogenesis could be blocked by hypophysectomy (Cross et al., 1982) which suggests that limbic effects on the immune system were mediated through the neuroendocrine axis. On the other hand, the centromedial as well as basolateral amygdala lesion-induced behavioral and immune effects were studied by Grijalva et al. (1990). According to the authors, although the centromedial-lesioned rats were overactive and the basolateral-lesioned ones were hypoactive in the novelty test no significant influence of the lesions on NKCC was found.

In the septal area, kainic acid (KA)-induced lesions resulted in decreased antibody production including IgG, IgA, while similar lesioning of the hippocampus resulted in elevated IgM and IgG antibody production, in response to ovalbumin challenge (Nance et al., 1987). The involvement of the medial septum in the cellular immune responses was reported by Labeur et al. (1991), who observed after electrolytic lesions of this structure up to a 25-day inhibition of T-lymphocyte proliferation induced by Con A, PHA, and PWN. Wetmore et al. (1994) found significant elevation of NKCC after kainic acid injection into the lateral septum only in female rats. According to Zach et al. (1999) the damage to the septum in the rat brain by electrolytic lesion

caused a decrease of the number of peripheral blood leukocytes, mainly cells exhibiting CD25 and CD45RA antigens. More recently, Jurkowski et al. (2001) have found that electrolytic lesions of the medial septum and the bed nucleus of stria terminalis (BNST) caused gradual depression of NKCC, which peaked on the 10th day after the lesion, followed by a recovery to the baseline on days 21 (medial septum) and 42 (BNST) postinjury. Neither change in NKCC after electrolysis in the septal dorsal, lateral and septohypothalamic areas, nor in the basolateral amygdaloid nucleus was found.

Reports of Deleplanque et al. (1994) have revealed that both striatal and mesolimbic dopaminergic pathways are asymmetrically involved in neuroimmunomodulation. The authors have found that after lesions of the striatum, proliferation of splenic lymphocytes was impaired only in the right-lesioned group. After lesions of the nucleus accumbens, no modification of T lymphocyte mitogenesis was observed however, splenic NKCC was depressed in left-lesioned mice in comparising with controls or right-lesioned animals. Devoino et al. (1997) have suggested that bilateral electrolytic destruction of the brain areas containing dopamine (DA) cell bodies (nuclei A9 and A10) as well as terminal regions of the nigrostriatal and mesolimbic DAergic systems (nuclei caudatus and accumbens) resulted in a considerable decrease in intensity of the immune response in rats immunized with SRBC. The most pronounced elevation in the concentration of DA and its metabolites was observed in nuclei caudatus and accumbens, hypothalamus, hippocampus, amygdala within 20 min following antigen inoculation. Recently, Chen et al. (2004) have found that lymphocytes contribute to KA-induced hippocampal neurodegeneration and that $CD4^+$ T cells and B cells may act effectively to halt and even prevent the lesion-induced neurodegenerative process.

2.2.6. The cortex

Neocortical-dependent functions, such as attitudes, hopes, spiritual resources, may neutralize the effects of extreme stress and thereby shape the immunologic mechanisms involved in maintenance of health. Lesions of the cerebral cortex suggested that CNS influences on immune responses may be also lateralized with the two hemispheres of the brain modulating one another. Brain asymmetry in neuro-immunomodulation has been previously demonstrated by unilateral neocortex ablation experiments or using a behavioral paradigm in mice (Renoux et al., 1983, 1987; Neveu et al., 1986, 1989; Neveu, 1992). The authors have reported that lesioning the left cerebral cortex resulted in altered T-cell number and function and NKCC, with no effect on B cells or macrophages. By contrast, lesions of the right cerebral hemisphere enhance T-cell function. These data yield interesting correlations with handedness and the increased incidence of early dyslexia, together with the development of autoimmune diseases in left-handed individuals. In view of the central environmental circumstances, including stressful life experiences, the immnomodulatory effects of the cerebral cortex could be an important link between psychosocial factors and alterations in immunocompetence.

Currently, Moshel et al. (2005) have shown that electrical stimulation of rats' left temporo-parieto-occipital cortex during their behaviorally active nighttime period causes increased circulating levels of T cells but not NK or B cells. Right-side stimulation, stimulation during the inactive daytime period, and left-side nighttime stimulation of adult thymectomized rats had no effect on circulating levels of T cells. Moreover, the investigators were careful to rule out changes in blood glucocorticoid levels before and after stimulation and found that a spinal cord block at T1 ablated the cell circulation response to left-side cortical stimulation. The authors have concluded that there is a direct neocortical influence on migration of mature T cells from the thymus mediated by the sympathetic nervous system and have proposed that a cortically derived neurothymic circuit regulates thymic production of mature $CD4^+$ and $CD8^+$ T cells.

According to Tuohy (2005), the Moshel study provides a new and insightful perspective for a more thorough evaluation of the relationship between the CNS and the immune system. In addition, it offers a new direction for therapy in immune disorders, namely, the potential use of cortical stimulation as a therapeutic adjunct for increasing thymic production of peripheral T cells in disease states. Immunity may be regulated substantially by individual sensory experiences and ultimately by one's own perceptions and thoughts.

2.2.7. Cerebellum

In the CNS, the cerebellum, probably owing to its traditional concept limited to the motor control, is less well studied in immunoregulation. However, the direct and bidirectional connections between the cerebellum and the hypothalamus have been indicated, which are named as cerebellohypothalamic and hypothalamocerebellar projections (Dietrichs et al., 1994; Haines et al., 1997; Cavdar et al., 2001a,b; Zhu et al., 2004). Moreover, it has been shown that stimulating cerebellar fastigial nuclei evoked in hypothalamic neurons either a post-synaptic response or a change in unitary activity via cerebellohypothalamic projections (Min et al., 1989; Katafuchi and Koizumi, 1990; Wang et al., 1997). Therefore it is possible that the cerebellum influences lymphocyte function via direct cerebellohypothalamic projections. Previously, Ghoshal et al. (1998) reported that the lesion of the vestibulocerebellum depressed the secretion of haematopoietic cytokines in tissue cultures of bone marrow and thymus, and decreased peripheral blood leukocyte concentration, neutrophil myeloperoxydase response and antibody titer to SRBC. The opposite effect to the suppressive influence of vestibulocerebellar lesions on immune function was observed currently (Peng et al., 2005). The authors found that the Con A-

induced lymphocyte proliferation and the NKCC were both significantly enhanced on days 8, 16 and 32 following the effective kainic acid lesions of the bilateral fastigial nuclei of the cerebellum in rats. According to the authors, cerebellar fastigial nuclei participates in the modulation of lymphocyte function and the hypothalamus and sympathetic nerves innervating lymphoid organs but not HPA axis are involved in this neuroimmunomodulation.

2.2.8. The midbrain periaqueductal gray (PAG)

A few studies have determined the specific brain region(s) involved in opioid-induced immunoregulation. In this respect, the periaqueductal gray (PAG) matter of the mesencephalon has been identified as the area of morphine-mediated, naltrexone-sensitive suppression of rat splenic NKCC (Weber and Pert, 1989). Suppression of splenic NKCC may be obtained by ventral PAG stimulation (Weber and Pert, 1990). Additional studies of Demetrikopoulos et al. (1994) revealed that while dorsal PAG stimulation did not alter mitogen responses or splenic NK activity in rats, stimulation of this region of the PAG produced a marked decrease in peripheral blood NK cell response. The authors suggest the possibility that the immune suppression obtained from dorsal PAG stimulation is due primarily to its aversive properties.

2.2.9. The blood–brain barrier (BBB), circumventricular organs (CVOs) and vagal complex (VC)

Some locations in the CNS are more desirable in the world of neuroimmune real estate than others (Banks, 2004; Marvel et al., 2004). According to Banks (2004), neuro-immunology is a special example of brain–body communication and an especially complex one. In the neuroimmune communication pathways cytokines are the major mediators. Circulating cytokines could enter the brain through areas with a poorly developed blood–brain barrier (BBB) (Banks and Kastin, 1985) or can be actively transported (Gutierrez et al., 1993, 1994). Saturable transport of cytokines across the BBB seem to be an established mechanism of communication between brain and immune systems (Banks et al., 2001).

The circumventricular organs (CVOs) include the pineal gland, the subfornical organ, the median eminence, the neural lobe of the pituitary, the area postrema, the subcommissural organ, and the organum vasculosum of the lamina terminalis (Weindl, 1973). In most regions of a typical CVOs, the majority of capillaries are not engaged in the formation of a BBB. CVOs are not homogenous, but consist of distinct regions, some of which can have a BBB (Johnson and Gross, 1993). The idea that cytokines can leak out of the CVOs and spread throughout the brain has largely been rejected and new evidence showing tanycytic barriers between CVOs and adjacent brain tissue in adults supports rejection (Peruzzo et al., 2000). However, CVOs are a likely route through which signals from the periphery area transmitted into the CNS by afferent and efferent nerves or translocation of substances (Ferguson and Marcus, 1988; Johnson and Gross, 1993).

The concept of afferent nerve transmission is well documented for vagus (Watkins et al., 1995) which provides another pathway for communication between the immune and nervous systems and has been extended to other nerves (Romeo et al., 2001). The recent paper by Marvel et al. (2004) emphasized that the dorsal vagal complex (DVC) brings together the CVOs (the area postrema) and the vagal afferents. But the DVC also contains regions that have an intact BBB which allows bidirectional passage of cytokines, immune cells, and other substances across an intact BBB. As the barrier pathways, the vagal input, and the CVOs are all represented in this small anatomical area, the area postrema could play a significant role in neuro-immune communication. Marvel et al. (2004) point out that the vagal pathway seems especially significant in promoting social withdrawal, Banks et al. (2001) shows that transport of IL-1 across the BBB is a key factor in memory impairment, and CVOs classically react to stimuli demanding immediate responses. According to Banks (2004) the relevance of pathway variations in the communicated message may ultimately be related to the type of immunologic insult which can utilize that pathway.

3. The immune system communication with the nervous system

For a long time, the brain was considered to be a privileged organ from an immunological point of view, owing to its inability to mount an immune response and process antigens. Although this is partly true, the CNS shows a well-organized innate immune reaction in response to systemic bacterial infection and cerebral injury (Rivest, 2003). There is compelling evidence to show that the immune system can communicate with the CNS and two-way communication between the CNS and the immune system (Besedovsky et al., 1983; Carlson et al., 1987; Blalock, 1989; Sundar et al., 1991; Watkins et al., 1995; Dantzer, 2004) serves as the foundation for the multidisciplinary field of psychoneuroimmunology. This immune-to-brain communication pathway triggers the production of a constellation of CNS-mediated phenomena, collectively referred to as “sickness responses” which is created by immune-to-brain signals activating CNS glia to release glial proinflammatory cytokines. The most recently recognized member of this constellation of changes is enhanced pain responsivity (Watkins and Maier, 2005).

3.1. The evidence for immune–neural communication

Recently, Rivest (2003) has shown that circulating LPS is able to cause a rapid transcriptional activation of genes encoding its receptor CD14 and Toll-like receptor 2, as well as a wide variety of pro-inflammatory molecules in circum-

ventricular organs (CVOs). A delayed response to LPS takes place in cells located at boundaries of the CVOs and in microglia across the CNS. Therefore, without having direct access to the brain parenchyma, pathogens have the ability to trigger an innate immune reaction throughout the cerebral tissue.

Initial evidence that the immune system may communicate with the CNS was obtained by Besedovsky et al. (1977) who observed that activation of the immune system is accompanied by changes in hypothalamic, autonomic, and endocrine processes. The authors demonstrated that 3 days after antigenic challenge, increased firing rates were detected in the ventromedial nucleus, but not in the anterior nucleus of the rat hypothalamus; sympathetic activity, indexed by noradrenaline turnover, was increased in the spleen and hypothalamus; and some immune responses, including those initiated by viral infections were associated with dramatic increases in blood levels of ACTH and corticosterone. Saphier et al. (1987) found changes in multiunit activity in the PVN as well as in the AH area following antigenic challenge. Furthermore, decreased NE concentration in noradrenergic neurons of the hypothalamus and in the brain stem occurred hours after the intraperitoneal injection of crude supernatants from ConA-stimulated spleen cells (Besedovsky et al., 1983).

Moreover, cells of the immune system can also synthesize and secrete several immunomodulatory hormones (e.g., luteinizing hormone, PRL, GH, CRH, ACTH, neuropeptides (enkephalins, endorphins), catecholamines (NE, E); Blalock, 1989; Carr and Blalock, 1991; Blalock, 1994). For instance, the lymphocytes (Harbour et al., 1987) and macrophages (Lolait et al., 1984) produce the endogenous opioid peptides and NE and E (Engler et al., 2005). Furthermore, human lymphocytes secrete the growth hormone (Hattori and Inagaki, 1998) and peripheral blood monocytes constitutively secrete the brain-derived neurotrophic factor (BDNF) which is up regulated by such inflammatory mediators as TNF-α and IL-6 (Schulte-Herbrüggen et al., 2005).

3.2. Cytokines as mediators of immune–neural interactions

Communication between the periphery and brain takes place via both neural and humoral pathways. Cytokines released by activated immune cells, in addition to their role in regulating cellular interactions, are one means by which the immune system communicates with the CNS and thereby influences behavior. IL-1, IL-2, IL-6, IFN-γ and TNF-α influence activation of the HPA axis and are, in turn, influenced by glucocorticoid secretion (Munck and Guyre, 1991; Sternberg, 2001). Recognition of the role played by the local production of cytokines and their downstream messengers in the central nervous system opens important new vistas for understanding and treating non-specific neurovegetative and psychiatric symptoms of diseases.

Previously, several experiments have implicated IL-1 among the cytokines as a likely candidate for a key immunotransmitter, communicating immunological activation to the brain (Besedovsky et al., 1975, 1986; Schettini, 1990). Moreover, Berkenbosch et al. (1987) and Sapolsky et al. (1987) demonstrated that IL-1 directly stimulated CRH by hypothalamic CRH neurons in vivo. Interleukin-1 has been shown to influence hypothalamic neurosecretory activity and enhance the turnover of NE in the hypothalamus (Berkenbosch et al., 1987; Sapolsky et al., 1987; Dunn, 1988). Receptors for IL-1 have been identified in the hypothalamic–pituitary region, hippocampus and the dorsal raphe nucleus (Breder et al., 1988; Cunninham and De Souza, 1993). IL-1 is produced not only by monocyte/macrophages in the periphery circulation but also by a variety of other cells in CNS, including astrocytes and microglia (Fontana and Grob, 1984; Giulian et al., 1986). Furthermore, mRNA for IL-1β and TNF-α has been demonstrated in anterior pituitary cells (Koenig et al., 1990; Gatti and Bartfai, 1993; Abraham and Minton, 1997), and anterior pituitary cells secrete IL-6 (Spangelo et al., 1991; Vankelecom et al., 1993). In addition, receptors for IL-2 were found in the hippocampal formation (Araujo et al., 1989; Sarder et al., 1993; Beck et al., 2002). Currently, Beck et al. (2005) have shown that IL-2 deficiency results in altered septal and hippocampal cytoarchitecture, including decreased cholinergic somata which appears to be due to a failure in neuronal maintenance/survival that may be, in part, associated with changes in neurotrophins. Furthermore, Ching et al. (2005) revealed that intracerebroventricular injection of IL-1β as well as IFN-γ and TNF-α induced infiltration of leukocytes identified as neutrophils into the brain tissue (blood vessels of the brain and cortex) between 8 and 72 h after the injection. According to the authors, IL-1 but not IFN-γ or TNF-α receptor located on the CNS endothelial cells, appeares to be important for the recruitment of leukocytes across the BBB.

It became evident that peripheral cytokines act indirectly on the brain. They trigger the production of cytokines in the brain parenchyma itself (Laye et al., 1994), with a possible relay at the interface between the internal milieu and the brain, represented by endothelial cells and circumventricular organs (Konsman et al., 2002). For example, cytokines released from activated immune cells can induce effects in the CNS by several possible mechanisms. Cytokines may enter the CNS at sites where the BBB is absent (Banks and Kastin, 1985; Gutierrez et al., 1993, 1994) or by carrier-mediated transport mechanisms, or they may induce their effects by binding to cerebral vascular endothelium and inducing the generation of central mediators (Watkins et al., 1995).

There is also a growing body of evidence to show that cytokines may exert their effects directly on the CNS by stimulating peripheral afferent neurons (Watkins et al., 1995; Dantzer et al., 1998; Goehler et al., 2000). Such mechanisms would allow the immune system to communicate in general events regarding immune responses to the

CNS. Also immune cells that produce cytokines can themselves cross the BBB to release their mediators centrally (Weller et al., 1996). Finally, the vagus nerve provides another very important pathway by which peripherally generated cytokines or cytokine-activated signals reach the brain (Fleshner et al., 1995; Goehler et al., 1997; Marvel et al., 2004). Currently, there is no direct evidence to support the hypothesis that activated lymphocytes communicate clone-specific information to the CNS (Jones, 2002). However, the phenomenon of immune conditioning (Ader et al., 1995; Ader, 2003) may provide indirect evidence that such a pathway exists.

Several studies have now shown that cytokines, chemokines, and selectins are directly involved in the recruitment of leukocytes into the CNS through the BBB (Betmouni et al., 1996; Minghetti et al., 1999; Bernardes-Silva et al., 2001; Proescholdt et al., 2002) which is involved in host defence against CNS infection (Borges, 1992; Patterson et al., 2002) and in CNS injuries resulting from immune activity inside the nervous tissue. Because inflammatory cytokines have the ability to induce the production of selectins and chemokines, they may be the initiators of leukocyte transmigration (Read et al., 1995). A study by Schiffenbauer et al. (2000) showed that the presence of the type I IL-1 receptor (IL-R1), but not the TNF-α signaling, was required for the recruitment of leukocytes in CNS tissue in a mouse model of EAE, suggesting that a IL-1R1 may be required for leukocyte recruitment in CNS tissue. It is possible that cytokines, probably through IL-1, first have to induce relevant cellular changes in endothelial cells prior to the induction of leukocyte infiltration. It has been shown that intracerebral injection of IL-1 increases the production of P-selectin on brain endothelial cells, which is critical for IL-1-induced neutrophil infiltration (Bernardes-Silva et al., 2001). It has also been postulated (Del Maschio et al., 1996) that IL-1 stimulation leads to the disorganization of the vascular endothelial-cadherin/catenin complex, thereby disrupting tight-junctions of vascular endothelial-cells. It has been observed that CNS IL-1 expressing cells are often microglia (Van Dam et al., 1992, 1995; Buttini and Boddeke, 1995). Therefore, it is possible that another consequence of cytokine-endothelium interaction is the production of endothelial mediators that elicit IL-1 production by microglial cells. According to Ching et al. (2005) IL-1 produced by microglia could, in turn, further stimulate endothelial cells resulting in a positive feedback circuit that amplifies the stimulation to endothelial cells. Such endothelium–glia interaction may contribute significantly to cytokine-induced leukocyte infiltration.

At present, in our understanding of cytokine-induced sickness, the cytokine pattern is likely to be distal to the phenomenon under consideration, and the proximal factor is certainly represented by those receptor molecules that decipher the molecular nature of microbial pathogens, so-called pathogen associated molecular patterns or PAMPs (Akira et al., 2001) at the membrane level of cells of the immune system. Recent evidence shows that the immune system can recognize broad categories of antigens and can tailor immune responses accordingly. Such an effect appears to be mediated at a local level by, at least in part, Toll-like receptors (TLR). According to Dantzer (2004), the description of the intracellular machinery that mediates the effects of cytokines on their cellular targets, and the way these signaling pathways cross-talk with each other and other ones activated, e.g., by growth factors, is the way science progresses. According to the author, a complete description of psychological effects that are mediated by fully understood molecular machinery is a new appreciation of the interactions between behavioral, neural, endocrine, and immune processes.

4. Conclusions

There are bidirectional circuits between the CNS and immune system. The CNS can communicate with the immune system via endocrine outflow from the CNS and by sympathetic innervation of the lymphoid organs. Although, the immunosuppressive effect of parasympathetic cholinergic system has been recently shown. On the other hand, the cytokines transmit specific signals and information from the immune system to CNS. Moreover, current findings indicate that the pathogens have the ability to trigger an innate immune reaction throughout the cerebral tissue without having direct access to the brain parenchyma. Such communication suggests an immunoregulatory role for the brain and a sensory function for the immune system. The mutual functional relationship between the CNS and immune systems is intensively studied with the perspective of the pharmacological control of immunity through the modulation of selective brain functions in clinical practice. The “immunoactive” brain areas include the hypothalamic nuclei, “brain reward system”, limbic structures, cortex, midbrain periaqueductal gray matter, cerebellum, circumventricular organs and vagal complex. The brain structures related to positive reinforcement (“brain reward system”), positive attitudes and hopes (limbic structures and neocortex) have beneficial effect on the immune response which may neutralize the effects of extreme stress and offers a new direction for therapy in immune disorders.

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