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Immunology and neurology

■ **Abstract** The classical field of neuroimmunology deals with the immune response in infectious, autoimmune-mediated, ischemic, degenerative, traumatic, and neoplastic diseases of the nervous

system with a major focus on immune-mediated demyelination. Recently more and more evidence points to a broader interaction between the immune and nervous systems via morphological connections, shared signal molecules and common mechanisms of signal transduction. Consequently, immune processes affect nervous functions and vice versa under both physiologic and pathologic conditions. This includes neuroendocrine (hormonal) and vegetative (neurotransmitter-mediated) influences on the immune response in-

cluding conditioned immunostimulation and immunosuppression (neuroimmunomodulation) as well as effects of immune mediators (cytokines) on neuronal and psychic functions (psychoneuroimmunology). These findings have a strong impact on future strategies for the treatment of somatic as well as psychiatric diseases.

■ **Key words** immunological privilege · HPA axis · neural and immunological synapses · neurotransmitter and cytokine receptors · electroimmunology

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Is the central nervous system an immunologically privileged organ?

The central nervous system (CNS) and the immune system have traditionally been regarded to be morphologically and functionally separated thereby protecting the CNS from immune attack. The brain was called an “immunologically privileged site” similar to the eye, the testis and the placenta [3, 4]. This view was supported by the following findings: (1) the existence of a blood-brain barrier (BBB) [46], (2) the expression of pro-apoptotic molecules at the BBB, (3) no expression of major histocompatibility complex antigens on nerve cells, and (4) no occurrence of professional antigen-presenting dendritic cells in the CNS. However, recently the concept of the brain as an immunologically privileged site has been challenged by additional findings such as (1) the existence of an extended lymph drainage of the CNS [13] (Fig. 1), (2) the regular passage of T and B lymphocytes through the BBB [21], (3) the identification of the cere-

brospinal space as an immunological compartment. Therefore, the CNS can at best be regarded as a relatively immunologically privileged organ.

Immune response in the nervous system

Immune responses within the nervous system are the subject of classical neuroimmunology, which has also been termed “immunoneurology” [11]. It is directed to the investigation of neuroimmune diseases that involve physiological immune responses against neurotropic infections as well as autoimmune responses against central myelin, as in multiple sclerosis (MS), and peripheral myelin, as in Guillain-Barré syndrome (GBS). In addition, the discipline investigates autoimmune responses in antibody-mediated disorders of the neuromuscular junction and in idiopathic inflammatory myopathies as well as immunological aspects of ischemic, degenerative, traumatic, and neoplastic diseases of the nervous system (Table 1, Fig. 1) [2, 28, 37, 54, 57, 58].

JON 2002

Fig. 1 CNS specific immune response is enabled by lymph drainage of the brain and spinal cord (adapted according to [13, 19])

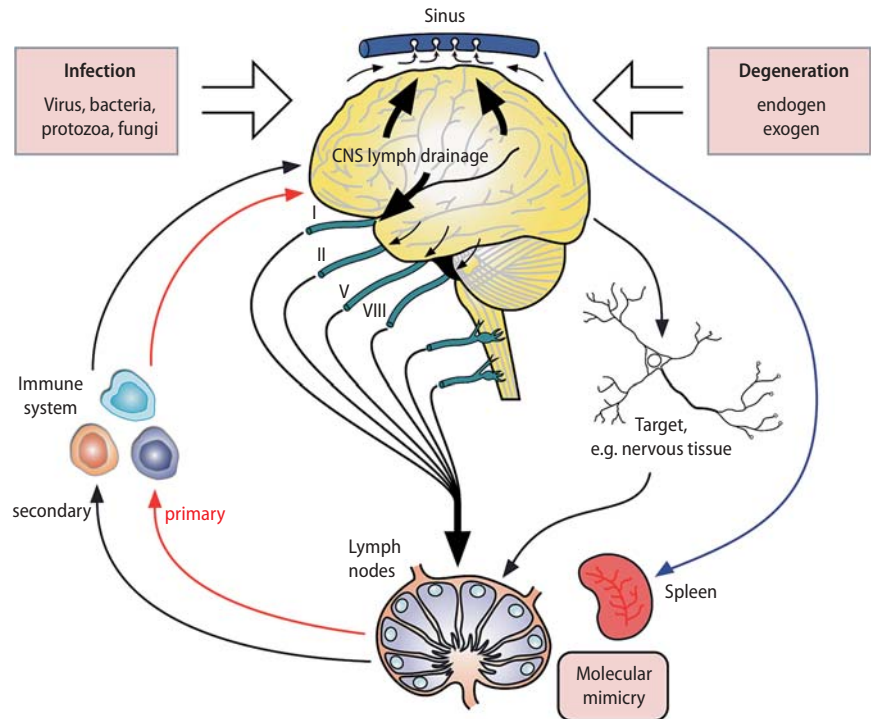


Table 1 Topics of classical neuroimmunology

1. Neuroinfections:

Encephalitis, encephalomyelitis, meningitis, polyradiculitis or polyneuritis caused by bacteria such as *Borrelia burgdorferi*, *Clostridium tetani*, *Clostridium botulinum*, *Treponema pallidum* and various coccoid and rod bacteria, viruses such as HIV, rabies, herpes, measles, mumps, Coxsackie, JC, RS and polio virus, prions and protozoa such as *Toxoplasma gondii*, *Trypanosoma brucei* and plasmodia.

2. Autoimmune diseases:

Multiple sclerosis, acute demyelinating encephalomyelitis (ADEM), Guillain-Barré-Strohl syndrome, chronic immune-related demyelinating polyradiculoneuropathy (CIDP), myasthenia gravis pseudoparalytica, Lambert-Eaton myasthenic syndrome, dermatomyositis, polymyositis, inclusion body myositis, vasculitides and collagenoses.

3. Other diseases with accompanying immune reactions:

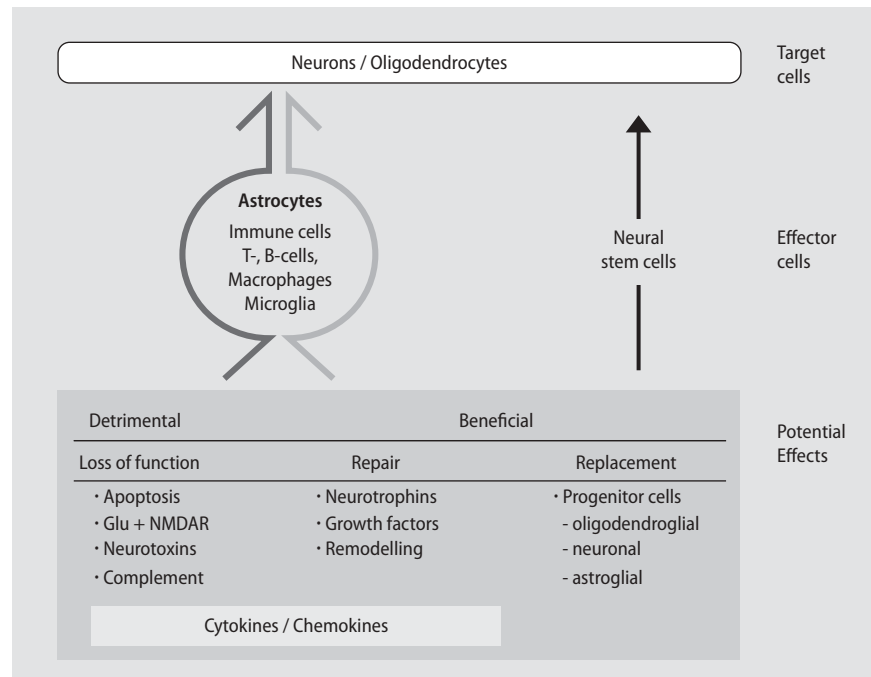
Neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, Huntington's disease and Lou Gehrig's disease (amyotrophic lateral sclerosis), cerebrovascular diseases such as stroke and intracerebral haemorrhage, neoplastic diseases such as primary brain tumours, leukemias and lymphomas, paraneoplastic syndromes, traumata such as spinal cord injury, and psychic diseases such as schizophrenia, major depressive disorder, epilepsy and narcolepsy.

The autoimmune reactions in the nervous system have traditionally been regarded to be hazardous and immunosuppression was, therefore, the prevailing therapeutic strategy. However, there are two major challenges against this strategy: (1) Neuroinflammation is dependent on the local density of autoantigens and vascularisation, and in its chronic form it is compartmentalised behind the blood-brain barrier thereby escaping from any systemic therapy including bone marrow transplantation [25]. (2) Autoimmune responses may involve neuroprotective aspects in inflammatory as well as in non-inflammatory neurodegenerative, traumatic and ischemic diseases [4, 31, 45, 50]. This is exemplified by the heterogeneity of pathogenetic and repair mechanisms in MS (Fig. 2). On the other hand, neurological diseases which are not regarded to be primarily im-

mune-mediated may nevertheless involve immune activation contributing to their pathogenesis according to the neuroimmune axis concept [35, 38]. In contrast, traumatic brain and spinal cord injury as well as stroke can also lead to CNS-induced immunodepression (CIDS) thereby increasing susceptibility to infection [30].

A special aspect of the immune response relates to the immunological dominance of certain microbial antigens that may not prevail quantitatively among the structural components of the microbes, but that may mimic organ-specific self antigens of the host. This phenomenon has led to the theory of the immunological homunculus (immunculus) as proposed by Irun Cohen and co-workers [8, 12, 20, 34]. According to this concept, inadequate regulation of anti-microbial immunity

Fig. 2 Immune factors regulating destruction and regeneration of nervous tissue in MS (adapted according to [19]). *Glu* glutamate, *NMDAR* N-methyl-D-aspartate receptor



can initiate and perpetuate autoimmune diseases; the treatment of which should strengthen regulatory (suppressor) cells by active measures such as T cell vaccination and anti-idiotypic antibodies, whereas effective anti-infectious immunity should be achieved by selective vaccination against microbial epitopes lacking molecular self mimicry.

Finally, neuroimmunology is also dealing with the interesting finding that immune cell activation involves changes in the transmembrane potential, which are mainly due to altered K^+ currents [9, 51] and can be manipulated by K^+ channel blockers [52]. This field of investigation is termed “electroimmunology” [10] and findings may have impact on future therapeutic strategies in autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and diabetes mellitus [5, 40].

Major aspects of classical neuroimmunology will be discussed in the following articles of the present issue of *Journal of Neurology*.

Interactions between the immune and nervous systems

The immune and nervous systems build up structural and functional networks of their cellular components that communicate via soluble factors and cell-cell contact, respectively. The basic structure of the cell-cell contact follows the same principles in both systems, i. e. the neuronal synapse and neuromuscular junction find their analogy in the immunological synapses between helper T lymphocytes and antigen presenting dendritic

cells and between cytotoxic T cells and their target cells, respectively [14] (Fig. 3). Both types of synapses even share the same matrix molecule agrin [22]. Two other structures that enable direct cell-to-cell communication in both the immune and nervous system are gap junctions [16, 29, 32] and tunnelling nanotubules [41, 56].

But how do both systems communicate with each other? A classical route is the cytokine-hypothalamic-pituitary-adrenal (HPA) axis, whereby cytokines such as the interleukins IL-1, 2, 6, 11 and 12, the tumour necrosis factor- α (TNF- α) and the interferon- γ (IFN- γ) induce the release of glucocorticoids, which in turn control the production of cytokines by immune cells [6, 7, 17] (Table 2, Fig. 4). However, neural influences on immune response can also be mediated directly via neurotransmitters and neuropeptides [26, 33], which may be released into synapse-like nerve-lymphocyte connections that fulfil the main criteria of neurotransmission [1, 15] (Table 3). This may also have impact on therapeutic intervention in inflammatory diseases. For example, electrical stimulation can prevent excessive inflammation in sepsis via inhibition of macrophage TNF- α release [55]. Other findings of neurotransmitter effects on immune cells are controversial. For example, reported modulation of T lymphocyte activation by dopamine [26, 42] was not confirmed by experiments under anti-oxidative protection [53]. Caution is also advised, if findings of receptor expression on immune cells are interpreted in the context of nerve-immune cell communication (Table 3). A special aspect of nerve-immune cell interaction concerns the influence of visible light on the immune system (photoneuroimmunology) [36].

Fig.3 Similarities between neural and immunological synapses (adapted according to [14, 47]). *APC* antigen-presenting cell, *CD2AP* CD2 adapter protein, *NMDAR* N-methyl-D-aspartate receptor, *PSD95* postsynaptic protein 95, *TCR* T cell receptor

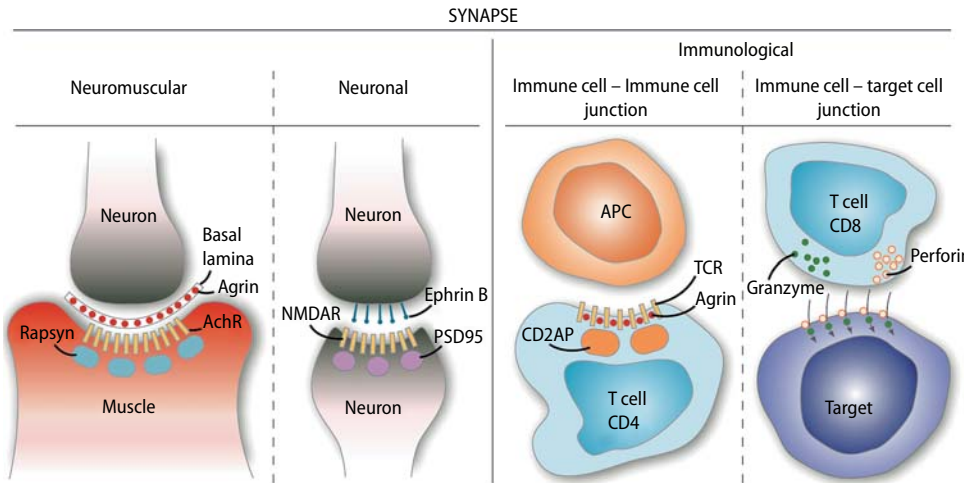


Table 2 Mutual interactions between immune and nervous systems

1. *Neural influences on the immune system* (neuroimmunomodulation) by neuro-transmitters (e. g. acetylcholine, norepinephrine, serotonin, histamine, glutamic acid, gamma-aminobutyric acid), by neuropeptides (e. g. adrenocorticotropin (ACTH), prolactin, vasopressin, bradykinin, somatostatin, vasoactive intestinal peptid (VIP), substance P, neuropeptide Y, endorphines, encephalines), and by neurotrophic growth factors (e. g. nerve growth factor (NGF), ciliary neurotrophic growth factor (CNTF)).
2. *Hormonal influences on the immune system* (neuroendocrine immunomodulation) by endocrine hormones (e. g. epinephrine and glucocorticoids).
3. *Influence of visible light on the immune system* (photoneuroimmunology).
4. *Modulation of nerve cell functions by immune and inflammatory mediators* (e. g. the cytokines tumor necrosis factor- α , transforming growth- β and interleukins, the chemokines, the interferons and reactive oxygen and nitrogen species).
5. *Pathological interaction between the immune and nervous systems altering cognitive and other psychic functions* (e. g. chronic fatigue syndrome and stress situations).

Fig.4 Schematic representation of the hypothalamic-pituitary-adrenal axis and its involvement in stress reactions of the immune system. *ACTH* adrenocorticotropin hormone, *CRH* corticotropin-releasing hormone, *IL-1* interleukin-1, *IL-1R* IL-1 receptor

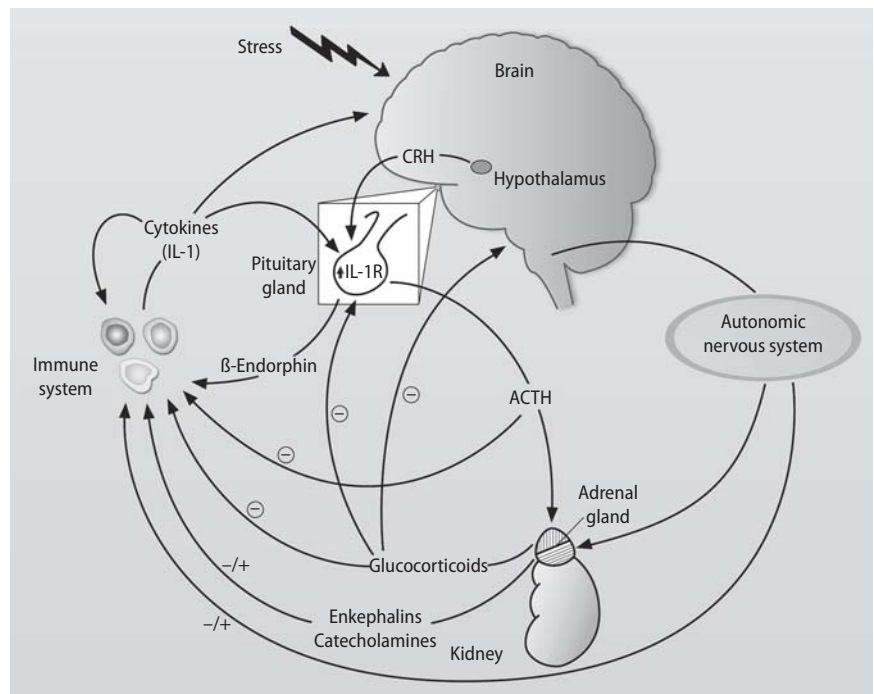


Table 3 Criteria of neurotransmission (according to [1])

1. Chemically specific nerve fibres and their compartmentation
Adrenergic > peptidergic, serotonergic > cholinergic
2. Neurotransmitter release and availability for interaction
Norepinephrin > neuropeptides (NPY, SP, VIP, VP, SOM, CCK, CGRP, ENK, END)
3. Receptors on target cells
 β_2 -adrenergic > peptidergic
4. Functional effects
Second messenger induction, expression of surface molecules, cytokine production, antibody production, cytotoxicity, migration, mitosis

However, caution is advised concerning interpretation of receptor expression by lymphocytes!

1. Real receptors?
Saturation, substitution, stereospecificity, second messenger coupling
2. Restricted expression
Specific compartmentation, specific cell cycle stage, specific stage of differentiation
3. Artificial up-regulation
Cell culture = denervation (supersensitivity)
4. Epiphenomenon of gene expression
leakage transcription

Question: Which cells use which transmitter and which signal pathway in which (organ-) system in which situation?

Another aspect of neuro-immune interaction relates to effects of immune mediators on glial and nerve cell functions, which have been documented for cytokines such as TNF- α , various interleukins and IFN- β [18, 23, 43] (Table 2). Under physiological conditions the mutual interaction between the immune and nervous systems appears to stabilise the homeostasis of the organism as a whole. However, if disturbed it may lead to pathological reactions such as stress and chronic fatigue. Moreover, immune-mediated neurological diseases influence the cognitive and other psychic functions of the patients and have a major impact on coping with the disease. Investigation of these aspects of neuro-immune interac-

tion and their therapeutic consequences is subject of the emerging discipline psychoneuroimmunology [24, 27, 44, 48, 49]. By involving the influences of emotions and strong mental activities on immune activities even a concept of psychoelectroneuroimmunology has been proposed [39]. Many of the aforementioned aspects of neuro-immune interaction will be covered by the following articles of the present issue of *Journal of Neurology*.

■ **Acknowledgement** The authors are most grateful to Verena Reimann for providing the clearly arranged and easily memorable artwork which she produced by complying patiently with long lasting tedious change requests.

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