Shot report

IMMUNE FUNCTIONS OF THE BRAIN

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Integrative activity of all brain sections results in the most surprising among all neurobiological phenomens - psychics. Besides this unique brain function, another one was determined - a participation in very complicated process of immunity. The concepts about the role of a brain in induction and regulation immune responses underwent radical changes last years. It was found that cerebrospinal fluid (CSF) is settled with T- and B-cells, which are not homogenous, subdivided into subsets (subpopulations), perform specific immune functions and are able to develop a local immune response in CSF and CNS (6). Subpopulations of T- and B-lymphocytes are programmed for certain immunological functions (1,5,6). Functional characteristics of blood and CSF (5,6) lymphocytes are almost identical. In health and disease of CNS there were found immunoglobulins (Ig) of various classes. There are evidences for a local synthesis of IgG in CNS. IgG synthesis has been reported in more than 90% patients with multiple sclerosis and subacute sclerosing panencephalitis. Ig and neurotransmitter synthesis by cells of CSF was shown (2,5). Thus, occurring in CSF cell populations and proteins take part in generation of various immune responses and realize the immunological surveillance in subarachnoid space, i.e. form immune barrier of the brain.

Also non-lymphoid ones: neuroglial cells (astrocytes, oligodendrocytes, microglia) and endothelial cells of brain vessels take part in immunological reactions in CNS. The studies have shown that astrocytes function ate as auxilliary cells mediating the immune reactions in brain tissue (2,3,6). Like macrophages astrocytes can synthesize and secrete interleukin-1 (IL-1). It is established that astrocytes in patients with multiple sclerosis can present antigens to T-cells and stimulate their proliferation during sensibilization and turning into cytotoxic lymphocytes. It was found that prostaglandins produced by astrocytes exhibit neuromodulating function. Produced by T-lymphocytes interferon induces marked increasing of antigen expression on glial cells of the brain *in vivo* and *in vitro* and results in appearance of la-antigens on astrocytes. As a result, glial cells can induce immune reactions and aquire sensitivity to lyses by cytotoxic T-lymphocytes. It is also shown that glial cells can induce interferon to be considered as one of the mediators taking part in immune response. Cytotoxic cytokines against oligodendrocytes were found. These cytokines seem to take part in processes of demyelinization in autoimmune diseases. Microglial cells are capable of stimulation, phagocytosis and expression on their surface Fc-receptors for Ig. In favour of immune functions of neuroglial cells serve evidences of their infecting with human immunodeficiency virus, which affects as it is known, only immunocompetent cells bearing CD4 antigen on the surface membrane. It was found that such cells in CSF are T-helpers, macrophages and monocytes while in itself nerve tissue - non-lymphoid cells of CNS: microglia, astrocytes and oligodendrocytes, which bear la-antigen on the surface and contain mRNA encoding CD4 protein.

Presence in astrocytes both classes of molecules of the major histocompatibility complex provides with it a full range of functioning as the cells, representing antigene T-lymphocytes. Binding of CD4-lymphocytes by astrocytes is the first stage of immune response initiation in CNS. Activated CD4-cells to produce interferon-γ (IFN-γ), which in turn induces astrocytes. These cells express HLA-DR antigens and produce IL-1, activating new T-cells. As a result there is an intensification of immune reactions in CNS (2,3).

For activation of CD4-lymphocytes, their physical binding with antigen-presenting cells - astrocytes of CNS, is necessary. Cells of vascular endothelium express la-antigens and can stimulate lymphocytes, taking active part in the development of immune reactions in CNS. In various CNS diseases the different types of

adhesive molecules on the surface of lymphocytes, monocytes, macrophages and endothelial cells were found. These molecules are binding firmly on the membranes of lymphocytes and granulocytes attracting them into inflammation foci of the brain tissue. Adhesion molecules occure on the membranes of endothelial cells in low concentrations; their expression appreciably increases in pathology of nerve system (multiple sclerosis, neuropathies), that promotes an in draft of immunocompetent cells to the inflammation focus.

By means of neuropeptides the brain regulates not only nerve and endocrine systems, but also immune system. The discovery of immunomodulating characteristics of neuropeptides has radically changed the ideas about mechanisms signal transmission from nerve system to immune one. Receptors to neuropeptides were found on the immunocompetent cells, that confirmed their participation in the realization of efferent link of neuroimmune interaction (1,4). On the cells of nerve system there were found the receptors to immunopeptides and cytokines, synthesized by immune cells, i.e. a functioning of afferent link in immune-nerve interaction was revealed. The opioids (immunopeptides), synthesized by nerve system, act on the receptors of nerve cells (3). At present, the existence of diffuse cell system regulating and coordinating a great number of special functions by means of peptide secretion is generally accepted.

A wide distribution of neuropetides outside the brain and presence in nerve tissue of hormone, considered in the past as hormones of peripheral endocrine glands, have under lied of conception about diffuse neuroendocrine system, which suggests an integration of nervous and humoral regulation both on the level of CNS and on periphery. Under normal conditions interrelation and interaction between nerve, immune systems of the brain and general immune, endocrine systems are realized by hormonal factors: mediators, hormones, neuro- and immunopeptides, cytokines, synthesized in cells of nerve, immune and endocrine systems and passing free through the intact blood-brain barrier.

Cytokines are heterogenous group of low molecular weight glycoproteins synthesized and secreted by various cells of immune and nerve systems, and realizing regulatory functions. Cytokines are binding with appropriate receptors on target cells and regulate activation, differentiation and proliferation of immunocompetent and other cells. It is shown that such cytokines (interferons, interleukins, tumor necrosis factor (TNF) and others) take part in functional regulation of endocrine, nerve and immune systems. Peptides and cytokines realizing neuro-immune-endocrine interaction have common receptors. Structural similarity of receptors was shown for IL-1 and IL-2, endorphins, ACTH. Cytokines are the main regulators of complex intercellular interactions in nervous and immune systems. Disturbance of regulatory processes mediated by cytokines can promote the rise of several severe diseases of nerve system (demyelinating and infections). It is of great importance that cytokines pass easily through the blood-brain barrier in both directions. They are the main mediators of neuro-immune interrelations (3).

Among numerous biological effects interferons (INF) is also its excitant action on neurons. Participation of INF-α in neuroimmune interactions has also been shown. INF-γ provokes an expression of la-antigen on astrocytes. INF has a wide spectrum of biological effects including psychophysiological ones. Interleukins (IL-1, IL-2) takes part in homeostasis regulation in CNS, regulates hypothalamus and hypophysis functions as well as level of endorphin, corticosteroid and ACTH in blood. IL-1, produced by astrocytes and microglial cells, induces secretion of hypothalamic corticoliberin which influences the functional activity of hypophysis. Analgetic effect of IL-lα evidences the neurotropic action of this cytokine. IL-2 and its receptors were found in brain extracts in viral and autoimmune diseases. Cells secreting IL-2 were found in the brain of health animals. IL-2 induces proliferation and differentiation of oligodendrocytes, increases reactivity of hypothalamic neurons (1,3,4), influences the functional activity of hypophysis. IL-6 produced in CNS promotes the differentiation and antibody-forming of B-cells migrating into foci of viral and bacterial affections of CNS. Like IL-6, tumor-necrosis factor (TNF-α) is produced in CNS by glial cells and is determined in CSF of patients with viral and bacterial meningitis, multiple sclerosis, AIDS-dementia and others. In aggravation of multiple sclerosis there is

increasing of TNF, its level being correlated with the course of disease.

Summarizing the above data it can be concluded that the brain realizes immune functions by means of three morphologically and functionally different subsystems: the first one is represented by lymphoid cells of CSF (T-, B-cells and their subpopulations), natural killer cells, monocytes and macrophages; the second one is represented by non-lymphoid cells of nerve tissue - microglial cells, astrocytes, oligodendrocytes and cells of vascular endothelium; the third subsystem is represented by humoral factors, biological active substances - mediators, peptides, cytokines and others. Thus, analysis and generalization of literature and our clinical-experimental data change our notions about the role of brain in immune response. The presence in the brain of high-effective set of lymphoid and non-lymphoid cellular elements and their products allows to consider that, besides the realization of very complicated psychical functions, the brain not only takes part in generation and regulation of immune response in CNS and general immune system, but also itself is one of the organs of immune system.

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ROLE OF IMMUNE DAMAGES IN THE NEUROLOGIC PATHOLOGY

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Cerebrovascular pathology still has an enormous impact on public health of every nation. It is ranking among the leading causes of serious disability. One of the most unfavorable forms of disability that has the greatest social value is dementia. Epidemiological studies have identified 46 persons with vascular dementia (7,3%) and 14 persons with probable Alzheimer's disease (1,2%), mean age 50,4±6,7 years. Identification of the main causes contributing to the development of dementia and elaboration of early preventive measures is the issue of great importance. Studies conducted give us an opportunity to define and analyze the factors influence on the development and outcome of cerebrovascular dementia and probable Alzheimer's disease. We believe that these researches will have increasing importance.

Recently object of research HLA of system were HLA antigens. HLA antigens were investigated in various human populations. After establishing the method of polymerase chain reaction, opportunities emerged to explore the different sections of DNA and the genes that are located in these sections. Molecular-genetic methods of research extremely enlarged our knowledge of alleles, especially those of class III and its polymorphism. The last hypothesis about HLA structure has been reviewed (6). Genes of class III in comparison to genes of classes I and II are not fully researched. Genes of class III are located in the space between genes of classes I and II of HLA system and have important biological functions (7). Investigation of polymorphism of genes of class III (HLA) system is of great importance for the problem of HLA and cerebrovascular pathology, as well as for problems of neurological and immunological memory and perspectives of rehabilitation of such patients (4). Recent investigation revealed a large number of new genes belonging to the class III (HLA) system.

Our aim was to determine the concentration of cytokines TNF-α, TNF-β encoded by genes A and B of the locus of TNF in blood serum and cerebrovascular fluid of patients