

PATHOPHYSIOLOGY

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Pathways of information exchange between immune and nervous systems**E. A. Korneva*

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An exchange of information between the immune and nervous systems, *via* main sympathetic and parasympathetic afferent and efferent ways of signal transmission providing the possibility of the constant dialogue between these systems. This article addresses new information about immune system innervation and its connections with the central nervous system. Vagal nerve appears to play a key role in this interaction. The antigen challenge induces cytokines production (IL-1, TNF α , IL-6, and IFN γ etc), which receptors are present on the peripheral neurons and terminals of *n. vagus*, which innervate many internal organs. These signals are transmitted to the neurons of central nervous system. Recent data are used to develop methods for correcting the functions of the immune system in allergic and autoimmune diseases, affecting the mechanisms of their regulation. For example, activation of parasympathetic system leads to suppression of the development of inflammation.

Keywords: neuroimmune interactions, neuroinflammation, inflammatory reflex, innovative treatment.

The fundamental studies in Neuroimmunophysiology are the keystones for development of new therapeutic approaches in treatment of infectious, allergic, oncologic and autoimmune diseases. The achievements in this field allowed approving new treatment methods for autoimmune diseases based on affecting afferent and efferent fibers of vegetative nerves.

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An exchange of information between the immune and nervous systems, *via* main sympathetic and parasympathetic afferent and efferent ways of signal transmission providing the possibility of the constant dialogue between these systems. The existence of such pathways and mechanisms of information exchange in these systems is crucial for any intersystem cross-talk. Many axiomatic literature data as well as some early studies evidence that the information about foreign protein appearance reaches CNS in a short time.

An important approach was the study of the number and localization of the activated neurons within the definite brain structures, *c-fos* gene expression, and the quantity of *c-Fos*-positive neurons evidencing their activation. The algorithm of these alterations is specific for definite antigen [1] as well as for reactions of orexin neurons (regarding their quantity in hypothalamic structures) [2]. The question about possibility to transfer information from the immune system to the brain *via* nerve pathways has not been considered for many years; hence nowadays studies in this area formed one of the main trends in the Neuroimmunology. The research, initiated in the late 20th century, allowed obtaining completely new information about immune system innervation and its connections with the CNS. One of the initial studies in this direction reported that the dissection of *n. vagus* abolishing *c-fos* gene expression in hypothalamic neurons caused by i/p injection of LPS or IL-1. That witnesses for the intracerebral input of information about antigen presence *via* vagal afferent fibers. After intravenous LPS injection, vagal dissection didn't alter brains neurons reaction to antigen.

New techniques, such as pseudorabies virus tracing, provided more advances in this field of neuroscience. This virus moves in retrograde way from the site of injection, for instance, from the spleen — to the brain *via* vegetative nerves fibers, infects the neural cell and moves through its processes reaching other neurons. The signal transduction from the nervous to immune system is realized *via* sympathetic nerve fibers innervating the spleen, thymus and bone marrow [3]. In general, this information reveals possible mechanisms of regulatory effects of the above mentioned brain structures, in particular hypothalamic ones, on the immune system functions. On the other hand, the participation of afferent vagal pathways in the transmission of the information about the bacterial antigen entry into the intestine [4] was confirmed. The antigen challenge induces cytokines production (IL-1, TNF α , IL-6, and IFN γ etc), which receptors are present on the peripheral neurons and terminals of *n. vagus*, i.e. the vagus nerve afferent terminals and neurons respond to cytokines' action, and these signals are transmitted to CNS neurons. The afferent vagal fibers end on the dorsal vagal complex neurons in the caudal part of the medulla oblongata. It is a model of informational process and information input from the immune to the nervous system *via* parasympathetic afferent pathways.

The LPS or IL-1 injection results in activation of VLM and NTS neurons that project directly to the PVH. Subdiaphragmatic vagotomy suppresses activation of PVH neurons.

It is known that some 80 % of the vagal fibers are afferent [5].

Wide distribution of receptors and afferent vagal fibers in such organs as liver, lungs, and intestine is an important condition for detection of foreign agents at the early stages of infection, since immune stimuli activate sensor terminals and neurons of parasympathetic ganglia.

The pattern of brain neurons activation after application of various antigens varies [6] that could result from the difference in signals entering the brain.

Since it became apparent that the information about bacterial antigens, LPS and inflammation is transmitted to the brain *via* afferent autonomic neural pathways, the speed

of this process is high and significantly depends on the speed of cytokines' production that are transmitters of signals about antigen exposure. It is possible that these electrical signals encode information about the specificity of the pathogen. If it is true, the CNS can determine not only the infection location, but also the nature of the pathogen [7].

Several mechanisms are shown as well to establish the passage of the information about antigen appearance in the blood through the blood-brain barrier.

If injected to the peritoneal or intestine, antigens activate *via* cytokines the vagal fibers that transfer the information to the brain. For instance, LPS injection leads to a fast elevation of TNF α . These signals can be transduced *via* the parasympathetic afferent fibers. However, the information about LPS introduced into blood is transmitted to the brain mainly *via* the sympathetic neural pathways.

The cross-talk between immune and nervous systems evolves, forming the brain cells response to the obtained information.

Activation of parasympathetic system leads to suppression of the development of inflammation.

Recent data are used to develop methods for correcting the functions of the immune system, affecting the mechanisms of their regulation, mainly that of parasympathetic nervous system, including the development of diseases of allergic and autoimmune nature [8].

Irritation of vagus nerve significantly decreases the quantity of CD4+ T cells infiltrating the brain and results in a remission of multiple sclerosis. This method is an effective therapeutic approach and is clinically used for the treatment of patients with multiple sclerosis [9], rheumatic and other autoimmune/inflammatory diseases.

Stimulation of vagus nerve suppresses septic shock in mice and increases their survival rate by 80 %, this phenomenon can be used for the treatment of sepsis.

In the last years medical bioelectronics has been developed and non-invasive methods of physiotherapeutic influences on nerve fibers (mainly on vagus nerve) with the help of pulsating ultrasound were created. This approach has demonstrated the effectiveness in treatment of inflammatory and autoimmune diseases [10].

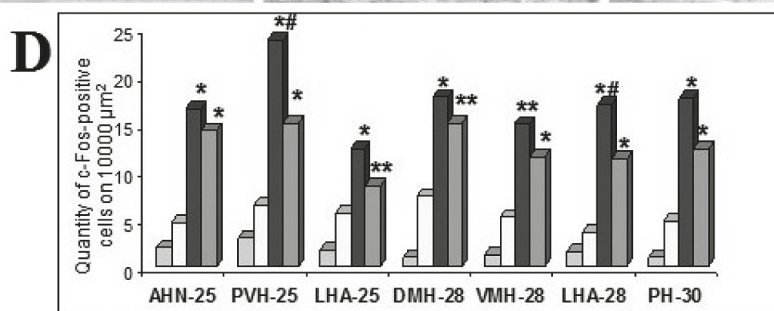
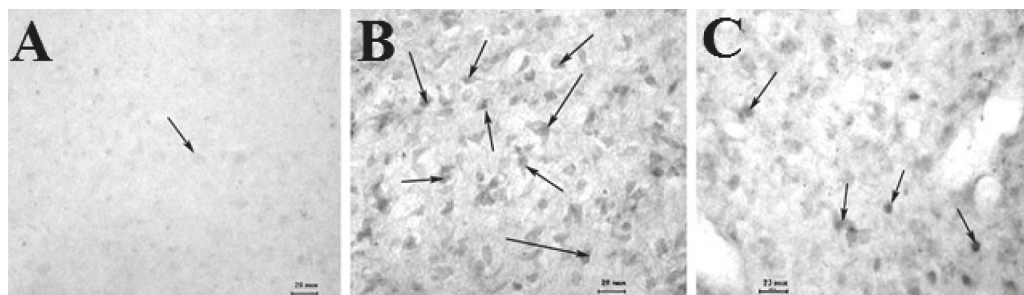
Thus, the analysis of the mechanisms of interaction between the nervous and immune systems already opened the possibility of developing new and effective methods for the treatment of inflammatory, allergic and autoimmune diseases, especially those torpid to cure.

The revolutionary nature of these approaches in Immunology is related to the obtaining of fundamentally new knowledge that reveals the mechanism of signal transfer to the brain in microbial exposure as well as brain responses, inhibiting or activating the infections process development, which is known as the reflex of inflammation.

Administration of such antigens as bovine serum albumin (BSA), tetanus toxoid and other proteins is known to cause neurons activation in the brain which is characterized by a certain pattern specific for the used antigen. It raises the question about the nature of information obtained from the immune system (figure).

The interiorization of antigen by antigen-presenting cells initiates the production and secretion of various cytokines by the immune cells. These molecules bind to receptors on the terminals and neurons.

Signals from the peripheral neurons come to ganglia, where they multiply the amount of c-Fos positive cells — the markers of activation. The electrical activity of the parasympathetic nerves also alters. Various cytokines cause certain different patterns of the electroneurogram changes, and these signals being transmitted to the brain [7].



After injections:

A- saline

B- LPS

C- BSA

D. Animals:

after injections:

□ - intact

□ - saline

■ - LPS

■ - BSA

* - $P < 0,01$; ** - $P < 0,05$ against their quantity in animals after saline injection

- $P < 0,01$ against their quantity in animals after BSA injection

Fig. Quantity of c-Fos-positive cells in hypothalamic structures of rat brain in 2 hours after LPS and BSA injections: A–C. Micrographs of brain slices at the level of the anterior nucleus of the hypothalamus (AHN) of the rat brain

The inflow of these signals to the CNS leads to activation of certain brain structures, first of all their parasympathetic nuclei, causing, as it was shown, an active production of c-Fos protein by the neurons of these structures. Then other nuclei, in particular, hypothalamic ones are involved.

If exposure to a particular antigen initiates the production of certain cytokines in a certain amount or ratio, the pattern of this reaction may be specific to the antigen.

Cytokine receptors are expressed on the cells of vegetative ganglia and on afferent nerve terminals and the response to them should depend on the nature of the acting cytokines, their number and ratio, these signals form a pattern specific for the antigen — “a bar code”, which is manifested by the peculiarities of electrical activity recorded on the afferent nerves.

Mechanisms of the immune response development enable researchers to create fundamentally new approach to optimize the treatment of diseases of various nature: i. e. inflammatory, autoimmune, and tumor ones.

The question about the nature of the information coming to the brain under the influence of antigen arises. At present, it is too early to conclude about the degree of antigenic specificity of this information patterns, as well as it would be too light-mindedly to neglect such a possibility.

References

1. Korneva E. A. Concluding Remarks. *Cytokines and the Brain*, Elsevier, 2008, vol. 6, pp. 567–570.
2. Perekrest S. V., Shainidze K. Z., Loskutov Yu. V., Abramova T. V., Novikova N. S., Korneva E. A. Immunoreactivity of orexin-containing hypothalamus neurons and the level of preproorexin gene expression in them after lipopolysaccharide administration. *Rossiiskii fiziologicheskii zhurnal imeni I. M. Sechenova*, 2011, vol. 97, no. 6, pp. 573–579. (In Russian)
3. Dénes A., Boldogkoi Z., Uherezky G., Hornyák A., Rusvai M., Palkovits M., Kovács K. J. Central autonomic control of the bone marrow: multisynaptic tract tracing by recombinant pseudorabies virus. *Neuroscience*, 2005, vol. 134, no. 3, pp. 947–963.
4. Goehler L. E., Gaykema R. P. A., Hammack S. E., Maier S. F., Watkins L. R. Interleukin-1 induces c-Fos immunoreactivity in primary afferent neurons of the vagus nerve. *Brain Res.*, 1998, vol. 804, no. 2, pp. 306–310.
5. Berthoud H. R., Neuhuber W. L. Functional and chemical anatomy of the afferent vagal system. *Auton. Neurosci.*, 2000, vol. 85, no. 1–3, pp. 1–17.
6. Korneva E. A., Shekoyan V. A. *Regulation of protective functions of the body*. Leningrad, Nauka Publ., 1982. 138 p. (In Russian)
7. Steinberg B. E., Tracey K. J., Slutsky A. S. Bacteria and the neural code. *N. Engl. J. Med.*, 2014, vol. 371, no. 22, pp. 2131–2133.
8. Ordovas-Montanes J., Rakoff-Nahoum S., Huang S., Riol-Blanco L., Barreiro O., von Andrian U. H. The regulation of immunological processes by peripheral neurons in homeostasis and disease. *Trends in Immunology*, 2015, vol. 36, no. 10, pp. 578–604.
9. Steinman L. Immunology of relapse and remission in multiple sclerosis. *Annual Reviews of Immunology*, 2014, vol. 32, pp. 257–281.
10. Bonaz B., Sinniger V., Pellissier S. Vagus nerve stimulation: a new promising therapeutic tool in inflammatory bowel disease. *J. Intern. Med.*, 2017, vol. 282, no. 1, pp. 46–63.

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