SPECIFICS OF PERCEPTION AND PROCESSING OF THE IRRITANTS IN THE FIRST AND SECOND SIGNAL SYSTEM UNDER THE ACTIVATION OF IMMUNE SYSTEM
ŠPECIFIKÁ VNÍMANIA A SPRACOVANIA STIMULANTOV PRVÉHO A DRUHÉHO SIGNÁLNEH0 SYSTÉMU PO AKTIVÁCII IMUNITNÉHO SYSTÉMU

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ABSTRACT
Introduction: The article discusses the issues of individual differences in the processes of higher nervous activity of a person in the processing of information signals of various signal systems. This issue is important both for understanding the mechanisms of interaction of various components in brain single integrative system, and for studying its relationships with other body systems, for example, the immune system.
Objectives: The aim of the research was to identify and analyze changes in the neurodynamic characteristics of a person in the aspect of studying the characteristics of processing features of irritants addressed to the I and II Signal System under conditions of functional activation of immune system.
Methods: 160 people were examined by immunological (CBC test, immunofluorescence method, ELISA) and psychophysiological studies after signing the Information consent. Its implementation was in accordance with the adopted methodology and manufacturer's instructions. The medical drug "Vilosen" (an extract of cattle thymus) was used as an immunomodulating agent. We studied the indexes of immunity system (the absolute number and relative content of leukocytes, lymphocytes, T-lymphocytes, T-helper/inducers, T-suppressors/cytotoxic, B-lymphocytes, the concentration of IgM, IgG, IgA) and neurodynamic properties (functional mobility of nerve processes, latent periods of sensorimotor reactions of varying complexity)
Results: According to our results, the improvement of the functional mobility of nervous processes while increasing the time of sensorimotor reactions under activation of cellular link immune system (the increase in the level of T-lymphocytes, $CD8^+$ cells and monocytes) were established. These changes were more pronounced when processing irritants of the I Signal System (geometric figures) than the II Signal System (names of animals / plants).

Key words: Immunity. Immunomodulation. Higher nervous activity. Sensorimotor reactions. Signal system.

ABSTRAKT
Úvod: Štúdia sa venuje problematike individuálnych rozdielov v procesoch vyššej nervovej činnosti človeka pri spracovaní informačných signálov rôznych signálnych systémov. Zverejnenie tejto problematiky je dôležité jednak pre pochopenie mechanizmov interakcie rôznych zložiek v jednom integračnom systéme mozgu, jednak pre štúdium jej vzťahu k iným systémom tela, napríklad k imunitnému systému.
Ciele: Cieľom štúdie bolo identifikovať a analyzovať zmeny v neurodynamických vlastnostiach človeka z hľadiska štúdia osobitostí spracovania stimulov adresovaných do signálnych systémov I. a II. za podmienok funkčnej aktivácie imunitného systému.
Metódy: Do prieskumu bolo zahrnutých 160 ľudí (21,6 ± 1,8 roka), ktorí podpísali informačný súhlas s účasťou. Imunologické (kompletný krvný obraz, imunofluorescenčná metóda, ELISA) a psychofyziologické štúdie sa uskutočnili v súlade so všeobecne prijatými metódami a pokynmi. Ako imunomodulačný prostriedok sa použil liečivý prípravok "Vilozen" (extrakt z týmusovej žľazy hovädzieho dobytka). Študovali sa parametre imunitného systému (absolútny počet a relatívny obsah leukocytov, lymfocytov, T-lymfocytov, T-pomocníkov / induktorov, cytotoxických T-supresorov, B-lymfocytov, koncentrácia sérových IgM, IgG, IgA), ako aj neurodynamické vlastnosti (funkčná pohyblivosť nervového systému). procesy, latentné obdobia senzomotorických reakcií rôznej zložitosti).
Výsledky: Podľa získaných výsledkov, sa bunková väzba systémovej imunity aktivuje použitím imunomodulačného činidla, čo vedie k zvýšeniu hladiny T-lymfocytov, buniek $CD8^+$ a monocytov, dôjde k zmenám vo fungovaní vyšších častí centrálneho nervového systému. Posledne uvedené sa prejavilo zvýšením úrovne funkčnej pohyblivosti nervových procesov a zlepšením schopnosti spracovávať signály rôzneho stupňa zložitosti. Zmeny boli výraznejšie počas spracovania podnetov I. signálneho systému (geometrické obrazce) ako II. signálneho systému (názvy zvierat / rastlín).

Kľúčové slová: Imunita. Imunomodulácia. Vyššia nervová aktivita. Senzomotorické reakcie. Signalizačný systém.

INTRODUCTION

The perception of the outside world is a rather complex process of processing many characteristics of an external object and related phenomena. The study of its features is important for understanding the adaptive reactions arising in response to the influence of environmental factors. The complex of sensory information about any object a person receives through the channels of the first Signal System (SS) of different modality (visual, auditory, tactile, taste analyzers) and, as a result, a perceptual (sensory) image of the object is created in the cerebral cortex. This sensory experience is individual to each person; it cannot be passed on to another individual. At the same time, the method of obtaining is common for humans and animals. In contrast, word, as an element of language and speech, is human-only phenomenon and is a discrete signal denoting a certain set of sensory signals, that is, a secondary stimulus ("signal of signal") of the second SS [1, 2]. To date, the issue of physiological mechanisms of SS of the higher nervous system has attracted the attention of researchers [3]. A promising area is the study of the problem of interaction of the SS with other components of a single integrative (functional) system of the body (with nerve centers, structures of the cortex and subcortex, cognitive functions).

The study of the relationship between the nervous and immune systems is particularly relevant, as it revealed the same receptor apparatus on neurons and immunocytes, capable of responding to the same ligands synthesized by these cells, and thus showed their functional unity. Priority in this relation is given to the nervous system. At the same time, the immune system is capable of altering the biophysiological activity of neurons while forming any immunological response, which is accompanied by functional rearrangements of individual neurons as well as entire parts of brain [4-7]. The possibility of influencing the state of the central nervous system (CNS) and the neurodynamic functions of the body through the use of substances with a neuromodulative or neuroprotective effect is widely used in immunocorrectional rehabilitation programs and for the prevention of certain pathological processes or conditions [8, 9].

The existence of individual and typological differences in functioning of the higher departments of the CNS should be taken into consideration, which determine the specific nature of interaction with the environment for each person. Despite the large number of studies examining neurophysiological and neurodynamic features, not all the aspects of individual traits of higher nervous activity (HNA) of a person have been revealed. According to different authors, HNA indicators can be influenced by various factors: Gender, age, general state of the organism [10, 11], and even the nature of information being processed (verbal or character-symbolic) [12]. At the same time, there is no sufficient research on the processing of stimuli addressed to different SSs. The aim of our study was to study examine the neurodynamic parameters in the aspect of determining the features of processing of stimuli of I and II Signal Systems under the influence of increased functional activity of the immune system's cellular link.

MATERIALS AND METHODS

The research was performed according to the World Medical Association's Declaration of Helsinki and Council of Europe Protocol of the Convention on Human Rights. Written informed consent was obtained from all the participants.

Study groups

The study involved 160 people at the age of 21.6±1.8 years old without acute or chronic illness. All volunteers were divided into control (n=80) and experimental group (n=80). In order to eliminate the "subjective factor", 40 participants ("placebo" group) were selected from the control group, who were injected with saline instead of the immunostimulating drug.

Assessment of neurodynamic functions

The study of individual neurodynamic properties (functional mobility of nerve processes (FMNP), latent periods of sensorimotor reactions of varying complexity) was conducted according to the method of M.V. Makarenko using the computer system "Diagnost-1" [13]. The essence of the technique is to differentiate the irritants that are transmitted to the monitor screen in a predetermined time mode by pressing the appropriate keyboard key corresponding to the desired signal. As stimuli related to the I Signal System, geometric shapes (square, triangle, circle) were selected; stimuli of the II Signal System are words indicating the name of an animal or plant. The FMNP was determined in the "feedback" mode by setting the highest rate of differentiation of positive and inhibitory stimuli with minimal exposure to their presentation at the test time. The study of neurodynamic functions was performed three times before immunostimulation and three times after completion of the course of the drug. It should be noted that the neurodynamic indicators of information processing have a functionally functional characteristic of human activity, which allows them to be used to determine the functional state of the body as a whole.

Assessment of cellular and humoral immunity

The following indicators studied the functional state of the immune system: total leukocyte count, relative and absolute number of lymphocytes, neutrophils and monocytes, T-lymphocytes and their subpopulations, B-lymphocytes and serum concentrations of IgA, IgM, IgG.

Peripheral blood was collected from each participant into EDTA test tubes in the morning before eating. Complete Blood Count (CBC) was measured using BC-3200 Hematology Analyzer (Mindray, China) according to the user's manual. Determination of the immunogram was carried out using the immunofluorescence method [14] and monoclonal antibodies to the surface receptors of these cells: $CD3^+$ to all T-lymphocytes, $CD4^+$ to T-helpers/inductors, $CD8^+$ to T-cytotoxic /suppressors, $CD19^+$ $CD22^+$ to B-lymphocytes (FITC-conjugated anti-human monoclonal antibodies firm Becton Dickinson, USA). Immunophenotyping was performed according to the manufacturer's protocol. After 30 minutes of staining, the cells were analyzed by a FACScan system (FACSCalibur flow cytometer, CellQuest software, Becton Dickinson, USA). The serum concentration of IgG, IgA, IgM were measured by ELISA [15] using a polystyrene plates MICROLON® (Greiner Bio-One, Germany) and the reagent kit "Immunoskrin-G, M, A-ELISA-Best" (Vector-Best, Russia). ELISA results were recorded spectrophotometrically on a PR2100 reader (Sanofi Diagnostics Pasteur, France) at 450 nm according to methodology and manufacturer's instructions.

As an immunostimulator an animal-derived drug Vilosen© ("Biopharma", Ukraine) was used, its main active substance is dialysate extract (purified) of the thymus of cattle. It stimulates the proliferation and differentiation of T-lymphocytes. One ampule of Vilozen© contains 0.02 g of powder extract, which was diluted by 2 ml of boiled water immediately before use and injected solution (5 – 7 drops) into each nasal cavity during the day (5 times a day). The drug was used according to the manufacturer's instructions for 14 days. Vilosen is used in medical practice as an anti-allergic immunomodulatory drug that is able to optimize the protective properties [16].

Statistical procedures

The data are expressed as arithmetic mean and standard error of the mean (M±m). Results were analyzed by using Mann-Whitney U-test, Pearson correlation coefficient (Microsoft Office Excel 2010, Statistica 6.0); differences with $p<0.05$ were considered significant.

RESULTS

The study of indicators of the immune system (Tab. 1) shows almost identical ($p>0.05$) levels of the main immunocompetent cells (leukocytes, lymphocytes, monocytes, neutrophils, T- and B-lymphocytes) in the study groups at the initial stage of the experiment.

Comparative analysis of the data from the study of neurodynamic functions (Tab. 2) indicates that there are no statistically significant differences between the mean group values of the neurodynamic parameters in the control and experimental groups

Table 1 Indexes of the immune system of participants in the control and experimental groups (M±m)

Indexes	Control group (n=80)	Experimental group (n=80)	Control group ("placebo" group) (n=40)	Experimental group (n=80)
	Before treatment	**Before treatment**	**After using saline solution**	**After using drug**
Leukocytes, $^*10^9$/L	6.8±0.12	6.5±0.78	6.8±0.2	6.9±0.1
Lymphocytes, $^*10^9$/L	2.2±0.1	2.0±0.6	1.9±0.14	2.3±0.52
Monocytes, $^*10^9$/L	0.36±0.05	0.3±0.01	0.34±0.06	0.39±0.04*
Neutrophils, $^*10^9$/L	4.1±0.03	3.9±0.05	4.2±0.03	4.0±0.03
T-lymphocytes, $^*10^9$/L	1.5±0.06	1.35±0.07	1.4±0.08	1.8±0.06*
T-helpers/inductor, $^*10^9$/L	0.55±0.06	0.6±0.03	0.58±0.04	0.55±0.09
T-suppressors/cytotoxic, $^*10^9$/L	0.32±0.02	0.33±0.07	0.33±0.04	0.49±0.05*
B-lymphocytes, $^*10^9$/L	0.36±0.02	0.42±0.2	0.37±0.05	0.41±0.1
IgM, g/L	1.02±0.04	0.84±0.2	1.04±0.04	0.89±0.2
IgA, g/L	1.46±0.08	1.55±0.3	1.5±0.1	1.65±0.2
IgG, g/L	6.3±0.2	7.5±1.2	6.0±0.3	7.3±1.5

** - level of validity of differences p<0.05 between initial parameters and post-immunostimulation level; ¤ - level of validity of differences p<0.05 between the experimental group and the "placebo" group.*

Table 2 Indexes of neurodynamic functions in the processing of irritants addressed to first and second Signal Systems (M±m)

Indicator	Control group (n=80)		Experimental group (n=80)		Control group ("placebo" group) (n=40)		Experimental group (n=80)	
	Before treatment		Before treatment		After using saline solution		After using drug	
	Figures	Words	Figures	Words	Figures	Words	Figures	Words
SVMR, ms	258.3±5.5	275.1±3.1	256.7±1.8	277.4±3.2	264.2±4.6	282.4±3.4	296.3±1.2*	289.5±4.3*
LP CR 1-3, ms	346.5±3.8	467.6±3.8	353.8±3.2	471.2±3.4	354.2±4.8	498.4±3.1	377.0±3.2*	484.2±3.1*
LP CR 2-3, ms	399.8±3.5	516.0±4.0	402.5±3.4	515.7±2.6	393.4±4.0	522.1±2.5	416.6±3.8*	519.0±2.8
FMNP, s	72.0±1.1	76.4±1.2	69.0±1.8	75.5±1.1	71.2±2.2	75.3±1.5	61.3±2.0*	63.2±1.2*

** - level of validity of differences p<0.05 between initial parameters and post-immunostimulation level; ¤ - level of validity of differences p<0.05 between the experimental group and the "placebo" group.*

at the initial stage of the experiment (before the use of the drug). Initially, no significant differences were found between the study groups in the results of testing for stimulus material categories, stimuli of the first and second signal systems. At the same time, in both the control and experimental groups, there was a tendency to increase the time of LP of sensorimotor reactions (SMR) and the time of the test to determine the level of FMNP in the tasks of processing stimuli addressed to the second signal system ("animal / plant name").

A study of systemic immunity state after immunostimulation in the experimental group revealed an increase in lymphocyte content (15 %; $p>0.05$), monocytes (26 %; $p<0.05$), $CD3^+$ (33 %; $p<0.05$), $CD8^+$ (48 %; $p<0.05$), increasing the concentration of IgM and IgA (6 %; 6.5 %; $p>0.05$) from the initial level of the indicators of this group. Compared with data from the "placebo" group, similar results were found: increased lymphocyte content (21 %; $p>0.05$), monocytes (14.7 %; $p>0.05$), $CD3^+$ (28 %; $p<0.05$), $CD8^+$ (48 %; $p<0.05$), $CD22^+$ (10.8 %; $p>0.05$), increasing concentrations of IgA (10 %; $p>0.05$), IgG (21 %; $p>0.05$) and a decrease in IgM concentration (14 %; $p>0.05$). Differences between B-lymphocyte content, IgG, and IgM levels are explained by different baseline values in these comparison groups. Therefore, the indicators influenced by "Vilosen" can be considered the content of monocytes, T-lymphocytes and their subpopulation of T-suppressors/cytotoxic.

We obtained the results that were not significantly different from baseline neurodynamic parameters and the indicators of systemic immunity of the control group in the "placebo" group.

As a result of the analysis of data obtained after the course of immunostimulation, we found significant differences in the sensorimotor response of the subjects of the experimental group from the initial level and compared with the data of the "placebo" group after the use of saline solution. An increase in the time of LP SVMR was observed when performing tasks with figures (39 ms; $p<0.05$) and, to a lesser extent, tasks with words (12 ms; $p<0.05$), compared to the initial level. There was also a more distinct increase from the initial level of LP CR 1-3 in the tasks with figures (23 ms; $p<0.05$) than when processing verbal stimuli (13 ms; $p<0.05$). Significant changes in the LP CR 2 – 3 were found only in tasks with figures: its value increased from by 14 ms ($p<0.05$) from the initial level. At the same time, we found a significant improvement in FMNP after immunostimulation. When comparing the average group values of the volunteers of the experimental group after activation of the cellular link systemic immunity, was found to reduce the time of performing this test. In addition, the FMNP index underwent major changes in the processing of stimuli of the second signaling system (initial: 75.5±1.1 s; after immunostimulation: 63.2±1.2 s; 16.3 %; $p<0.05$) than in the processing of stimuli of first the signaling system (initial: 69.0±1.8 s; after immunostimulation: 61.3±2.0 s; 11.2 %; $p<0.05$).

DISCUSSION

The conducted research shows the possibility of influence immunostimulation not only on the immune system, but also on the indicators characterizing the state of higher nervous activity of a person. According to the data obtained, the main changes in systemic immunity due to the use of the drug were an increase in the content of monocytes, T-suppressors/cytotoxic, IgA and IgG levels, which is an indicator of the activation of the cellular link of systemic immunity. The data obtained are consistent with similar studies that characterize "Vilosen" as a drug that effects the metabolic processes of T-lymphocytes (activation of their proliferation and redistribution of subpopulation composition toward increasing effector $CD8^+$ cells) [17, 18].

We also found a prolongation of the latent period of simple and complex sensorimotor response (mainly the reaction of choice of one of the three stimuli) on the background of activation of the cellular link of systemic immunity. Some authors claim that immune-hormones are capable of inhibiting the transmission of nerve impulse at the neuromuscular synapse [19-21], which was also manifested in the results of our study.

The improvement of functional mobility of nervous processes against background of the activation of cellular specific immunity, shown in our work, may be due to the fact that immunological reactions can cause functional rearrangements in the central nervous system and change the bioelectric activity of brain neurons [22]. It is known from the literature, that immunocytes are a source of various cytokines that can affect the activity of the nervous system, and lymphocyte membranes have receptors that, in turn, can perceive neurohumoral signals and thus participate in the implementation of an efferent response to neuroimmune interaction [23]. These ideas come from the position of the functioning of the neuroendocrine and immune systems as a single structural and functional system that provides adaptive responses in response to the changing environmental conditions [4, 7]. In our case, it is possible for interferons (except for interferon-g, which is not synthesized by either monocytes or T-suppressors/cytotoxic) and a neuropeptide, perhaps an S-100 protein, that is responsible for the learning process and facilitates interneuronal connections and adhesion of neurons [22]. There is also evidence that the increase in bioelectric activity of neurons is reflected in the increase in the maximum rate of mental processing load in the differentiation of positive and inhibitory signals [21].

Comparing the results of the time of the SMR reactions in the processing of different stimuli, we found that the average reaction time (SVMR, CR 1-3 and CR 2-3) for geometric figures (first-order signals) is less than for words (second-order signals), i.e. the predominance of the first SS was traced. Other researchers [24] obtained similar results. In addition, the results of our study showed that, against the background of the stimulation of the cellular part systemic immunity, the expansion of the time latent period of sensorimotor reaction and FMNP improvement had a more pronounced tendency in the processing of stimuli of the I signal system (geometric figures) than in the processing of stimuli of the II signal system (verbal names of animals and plants). In other words, during the immunostimulation, we observed the effect of improving the signal processing of the second signaling system, which may be explained by the corresponding functional changes in the immune system, accompanied by functional rearrangements in the central nervous system. Some studies have shown that the individual style of encoding information in the cerebral cortex (dominance of one SS over another, or their uniform interaction), creates prerequisites for the specificity of intellectual activity and mental capacity of a person, the formation of a certain type of personality ("artistic" or "mental") [25].

At present, the correlation of first-signal and second-signal methods of encoding and processing information is regarded as a problem of the hemispheric specialization of the brain with the fixation of a sensually-shaped form of presentation of reality on the right hemisphere, and verbal-logical – on the left. It is believed that there is a relationship between the speed of perception and the way information is processed, the nature of the stimulus and the hemispheric asymmetry of the brain, which affects the success of learning [26, 27].

We determined the correlation between the latent periods of sensorimotor reactions of varying complexity (SVMR, LP CR1-3 and LP CR2-3), the value of the time to perform the mental load processing test, which serves as an indicator of the properties of FMNP and indicators of the body's immune status (total number of leukocytes, monocytes, neutrophils, lymphocytes, T-lymphocytes of all subpopulations, the concentration of IgM, IgG, IgA in serum). The average negative correlation between the functional state of the central nervous system and the quantitative characteristics of immunocompetent cells was obtained: r = -0.6 between the monocytes number and the FMNP indices; r = -0.68 between the number of $CD8^+$-lymphocytes and the FMNP. The revealed correlations between the functional state of cerebral cortex (the level of functional mobility nervous processes) and the content of immunoregulatory cells ($CD8^+$-lymphocytes and monocytes) indicate the effect of immune system on the higher parts central nervous system and the body as a whole. Since FMNP is an indicator of the maximum speed of processing visual information, which characterizes the state of cerebral cortex, it can therefore be considered that the activation of immune system cellular link positively affects its state.

CONCLUSIONS

Our results require further study of the effect of activation cellular factors of systemic immunity on the nervous processes properties and the central nervous system functional state, on the features of perception and processing of information addressed to various Signal Systems, which in turn give a general idea of the functional capabilities of the organism. The data obtained are consistent with the current theory of immunoregulation of body functions, that is, the ligands of the immune system effect the work of all body systems, including the work of the CNS, which provides the processing of information coming from the external environment through the sense organs [13, 20]. Thus, it was found that the increase of activity of the cellular part immune system was accompanied by an increase in the level of functional mobility of the main nervous processes, which improved the capacity of higher CNS departments to process information of varying degrees of complexity.

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