FORMATION OF THE SYSTEM OF ANTI-STRESSOR REACTIONS AS A NON-SPECIFIC BASIS FOR HEALTH AND LONGEVITY

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Abstract

The proposed editorial article touches upon aspects of fundamental medicine associated with the discovery of systems of nonspecific adaptation reactions in the organism as a whole. It is shown that the key law of the organism’s response to the actions of the external and internal environment consists in the dependence between the reaction quality and the quantity (measure, intensity) of an acting factor. Revealed is the historical sequence of events in the development of the general adaptation reaction theory, beginning with the creation of the theoretical basis of pathology, i.e. description of the adaptation syndrome of stress reaction by Hans Selye, up to the intimately associated and logically continued studies and discovery of anti-stress-type reactions, namely, the reactions of training and activation, undertaken by Lyubov Garkavi, Maria Ukolova and Elena Kvakina. The characterization of archetypes of previously unknown, independent separate symptom complexes is given herein. The philosophy of adaptation discrete responses provided by the organism to different actions includes a higher stage of research progress, when it would be possible to understand the unique natural ability of periodic repetition of the adaptation reactions tetrad in a very wide range of action intensities. This is an adaptation software designed by Nature that is strategically important for the organism, including different levels of reactivity on a scale of absolute magnitude, and this phenomenon, like the D.I. Mendeleev’s periodic law, determines the possibility of forming the qualitatively different states at the same level (periods) and generating the states of the same name at different levels of reactivity (rows). The same name reactions of different levels differ in the nuances of their energy, peroxide and morpho-functional status that is important for conducting the controlled non-specific therapy in order to elevate the natural resistance of the organism. Activation therapy is a form of a targeted regulation of protective systems, namely, the nervous, endocrine and immune ones, that relies on laws, principles, programmed modes and biotechnology of accompanying therapy and functional rehabilitation that is all relevant for a new worldview: personalized medicine. This triggering mechanism works not in isolation from the individual processes of the organism’s response, but under due consideration of its identified adaptive response types, as a guideline in the treatment. This fundamental basis significantly improves the promising capabilities in solving such critical problems of medicine as oncology, cardiovascular diseases, aging, as well as pediatric, sports and space medicine. We hope that translation of the activation therapy developments into clinical practice will improve health of many people, without any limitations in space and time.

Keywords

Anti-stressor, Adaptation, Reaction of training, Activation, Stress

Imprint


More than 40 years have passed since Rostov scientists Lyubov Garkavi, Maria Ukolova and Elena Kvakina discovered an elegant, harmonious system of development of general non-specific adaptation responses to stimuli of different intensity [1, 2]. And this long period of time has become the best corroborating evidence for the validity of the laws and regularities revealed by the above discoverers.

In our high-density information environment in the technogenicity century, a highly fragile borderline between health and disease has been broken due to a growing flow of pathogenic influences: cosmic rays, radiation, electromagnetic smog, pollution of water, soil and air, new generations of viruses, nervous system tension, chronic fatigue, and stress itself. The streams of medical information abound with offers of super-precise, most accurate and reliable diagnostics and absolutely unique high-tech methods of treatment and stress removal.

We have at our disposal an expanded network of pharmacies, production of biologically active additives, take drops, medical drugs, immunostimulants, but remain still in the Stone Age considering our ignorance.
Is there an alternative to stressogenic environmental impacts and stress induction? Does the organism have its own mechanisms for choosing a response (reaction) of a quality other than stress?

The answer is as follows: it is the integrative activity of the organism, namely, its ability to produce various discrete states: not one, but a number of types of general non-specific adaptation responses or reactions, which depend on stimulation strength and intensity.

Many researchers dealt with these problems, but the solution was found in Montreal, Canada, by Hans Selye in 1936, and later, in 1975, in Russia, by L.Kh. Garkavi, E.B. Kvakina and M.A. Ukolova [3-8]. They used the most powerful tool of science: the dialectical approach, and revealed a quantitative and qualitative pattern between the strength of the acting stimulating factor and the general response, or reaction of the organism.

However, let us start from the very beginning. Hans Selye went down in history of medicine by breaking the psychological barrier of the primacy of quality and specificity in the organism’s response to a stimulus. Fascinated by the idea of non-specificity, he concentrated his attention on proving an almost incredible fact, namely, the stereotypical response by the organism to strong, excessively high functional loading, different in quality. This great scientific feat of the discovery of a stress reaction was the first attempt to create a theoretical basis for pathology accompanied by a description of stress as a general adaptation syndrome [3-8]. He applied a systemic approach and identified a connecting thread of events at different levels of the organization, noting changes in the hypophysis, thyroid gland, adrenal cortex, immune system, etc.

What occurs in the organism under stress? What mechanisms realize this state?

Upon a single action of the stressor (an extreme stimulus), a three-stage process develops under involving of all regulatory and actuating systems: the nervous, endocrine and immune ones. The nervous system is our radar and translator, which is the first to receive a signal, produce a differentiated evaluation of the stimulation strength and translate this information. Under stress, a state of an acute excitation appears in the brain that turns into a protective inhibition. The regulator of the internal environment, the hypothalamus, sends the releasing factors to the hypothysis through the portal system of blood vessels, and, as a result, an intensified synthesis of adrenocorticotropic hormone (ACTH) occurs against the background of a decrease in production of the other regulatory hormones (GTH, STH, TSH). The humoral phase of the stress realization mechanism begins. A lack of TSH weakens the functional activity of the thyroid gland. In the follicles, a thinning, and, in some cases, a complete desquamation of the epithelium takes place; the follicles lumen is expanded; a solidification of the colloid is observed due to a decrease in the production of thyroid hormones. The sex glands also reduce their activity. The amount of Sertoli cells, spermatocytes of order 1 & order 2 and spermatozoa decreases. In ovaries, the formation of primordial and mature follicles falls, and the count of yellow bodies increases.

The main events are found in the adrenal cortex, the main target of ACTH. The glomerular zone, which synthesizes mineral corticoids, dramatically narrows. An area of the fasciolar zone shows a manifolds increase; the cells therein are clarified and vacuolated due to an intensified secretion of glucocorticoids, ejection of which into blood initiates a pronounced reaction of inhibition in the thymic-lymphatic system: in the thymus, the lymph nodes and the spleen. In the thymus observed are the following involutive structural changes: a decrease in the number and sizes of lobules, thinning of the cortical layer by increasing of the cerebral one with accumulation of cysts. Similar changes are observed in the lymph nodes; the amount of follicles declines dramatically; the paracortical zone is thinned; the count of immune competent cells falls, and the Billroth’s strands contract. Finally, hyperplasia of the red pulp against the background of the involution of the white pulp takes place in the spleen. Rare and small follicles do not have typical zones filled with immune competent cells. The cellular composition of blood changes, and lymphopenia, aneosinophilia, neutrophilia and leukocytosis are observed. Since the time when Hans Selye described the symptom complex of stress, the blood formula is considered to be a signal criterion of GNAR (general non-specific adaptation reactions).

The result, or the product of the reaction is a drop in the resistance of the organism, a high energy consumption and suppression of protective systems.

It is important that, according to Selye, protection is achieved at the high expense, at the cost of damages.
and high energy expenditures. The organism’s resistance decreases in case of acute stress, and in case of the chronic one, when stressful effects take place again and again, the resistance becomes extremely low. And this is a non-specific background for any pathology.

However, in our lives, we deal with weak, medium and moderate influences in addition to the strong ones. Is it biologically reasonable to react to every stimulus in the same way?

Investigating the organism’s reactions to different stimuli, Russian scientists identified some other, qualitatively differing, integral reactions of the organism. They were independent, separate symptom complexes and other discrete states. It has been found that in response to a relatively weak influence, an adaptive symptom complex is formed, which is called “the reaction of training”; “the reaction of activation” is a response to a medium, intermediate between strong and weak, stimulus [9, 10].

It has been detected in the research that since the first hours of the delivery of a weak stimulus (applied influences as a weak electric stimulation of the hypothalamus through implanted electrodes, cannulas with neurotropic substances, permanent magnetic field, feeding with biostimulants of herbal and animal origin with the stomach pump), the reaction of training is produced by the organism with the anti-stress nature of the changes. The reaction of training is the response by the organism to weak stimulation. This reaction is of the daily rhythm type, and it covers certain stages within the 24-hour cycle and includes the stages of orientation, rearrangement and training. All the hierarchical levels are involved in this reaction: the nervous system, the hypothysis, the endocrine glands and the immune system. The symptom complex of the training begins with the formation of protective inhibition in the brain. Not only cortical, but also subcortical structures react to weak influences in a special manner. In the organs, connected with the hypothalamic-pituitary axis, the level of the releasing factors, which determine the corresponding level of secretion of the tropic regulatory hormones of the hypothysis without signs of suppression, gradually increases. In the phase of the humoral regulation the level of TSH contributes to a functional increase in the secretion of thyroid hormones of the thyroid gland within the range of the lower limit of the norm. The thyroid epithelium is cube-shaped. In this case, the follicles remain still poorly vacuolated, but no thickening of secretion is available. The gonadotropic hormone of the hypothysis produces a moderate stimulation of the functional activity in testicles and ovaries. In the adrenal cortex the glomerular zone returns to the norm with an adequate level of mineral corticoids secretion. However, in this case, the glucocorticoid activity of the fasciolar zone is at the upper limits of the norm that assures a sufficiently high anti-inflammatory potential in this reaction. The thymic-lymphatic system reaction against such a hormonal background is characterized by a slight increase in the thymus mass, the absence of disorders in the structure of the lymph nodes and the spleen. In peripheral blood, the level of lymphocytes is gradually elevated, and the count of eosinophils, monocytes and leukocytes is normalized.

The result of the reaction is a slow increase in the passive resistance, a predominance of anabolic processes over catabolism and an increase in the anti-inflammatory potential.

So, the same functional systems are involved, but the produced effects differ.

In response to the stimulus of the “medium” intensity, which is intermediate between the strong and the weak stimulation, the symptom complex of the activation reaction develops. The activation reaction was discovered by L.Kh. Garkavi in experiments with the use of electrodes implanted in the brain in animals [11-14]. She has detected that this is a general adaptation reaction to medium-intensity stimulation. This reaction also takes 24 hours and includes the stages of the primary and the stable activation. By the degree of expression of changes the activation is divided into the following subtypes: calm and elevated activation.

In the process of the formation of the activation reaction, the respective balanced and harmonious conditions for the functioning of the central nervous, the endocrine and immune systems are created. Schematically, the algorithm of changes includes some signs as follows.

The state of the brain is characterized by moderate physiological excitation. The processes of excitation and inhibition are well balanced, and the physiological activation of the hypothalamus releasing factors secretion, stimulating an increase in hypophyseal hormones, is noticed. However, their regulatory roles are distributed differently than under stress or training. TSH, STH and GTH are elevated with reaching the upper limits of the norm, and ACTH is in the usual status of the physiological norm. The algorithm of the
activation reaction humoral phase initiates the function of the thyroid gland with elevation up to the upper limits of the norm. At the same time, the cube-shaped epithelium often acquires a cylindrical shape due to an increase in the production of thyroid hormones. The follicles are filled with the vacuolated secretion. High functional activity of the sexual glands is observed: the processes of maturation of spermatozoa in the testicles and the formation of follicles, from primordial to mature, in the ovaries are intensified. The adrenal cortex reacts by the corresponding re-distribution of activity: in the expanded glomerular zone observed is a significant increase in the mineral corticoids secretion against the background of a moderate function of the fasciolar zone cells; the level of glucocorticoid hormones is normal. The reaction of the thymic-lymphatic system is characterized by hyperplastic changes in the lymphoid tissue. A significant increase in the number of lobules of medium and large sizes is observed in the thymus, the cortical zone of the lobules is expanded, and, due to the high content of lymphocytes, veils the brain substance. In the lymph nodes, the paracortical zone with a high content of mature lymphocytes is expanded. The count of follicles and Billroth’s strand filled with immune competent cells is increased. Observed are close intercellular contact interactions and the formation of the bioinformation structures, namely, the associates of lymphocytes and macrophages. In peripheral blood, the count of lymphocytes is elevated to the upper limit of the norm, at the same time the number of eosinophils may decrease slightly, and the count of monocytes increases and remains within the norm under the totally normal level of leukocytes.

All systems operate in the mode of physiological intensification without elements of tension and inhibition. As a result of the reaction, produced are the optimal conditions for an active increase in the organism resistance, a balance between the anabolism and catabolism processes, an efficient energy generation, i.e. a balance between expenditure and accumulation of the endogenous succinic acid, an activation of the enzymatic section, especially SDH, and an enhancement in the proinflammatory potential, i.e. the state of harmonious and effective vital activity of the organism.

The result of the excellent analytical work performed by the teams of our researchers was the discovery of the "Law of development of qualitatively distinct general non-specific adaptation reactions of the organism", Scientific Discovery Registration Certificate No. 158 issued by the Committee on Inventions and Discoveries at the Council of Ministers of the USSR to L.Kh. Garkavi, M.A. Ukolova and E.B. Kvakina [1]. This is a great discovery in the field of biology and medicine. If stress is a non-specific basis of pathology, then its alternatives are the training and activation reactions that serve as a non-specific basis for health, quality of life and longevity.

Thus, revealed was a pattern consisting of the following four reactions: training, calm and elevated activation, stress. The pattern has clarified the following issues: firstly, the discreteness of the organism’s states; secondly, the role of each reaction in regulating the resistance, i.e. the possibility of targeted control of the organism’s state.

However, the organism’s capabilities turned out to be much wider than expected. According to Russian Academician Researcher Molchanov, one should hear the rustling of a creeping snake and not be blinded by a great flash of lightning.

When carrying out experiments with different stimuli in a very wide range of doses, by identifying a gradation of reactions on the scale of absolute values, it was found that the pattern of development of the reaction sequence, namely, training, calm activation, elevated activation and stress, is repeated in different ranges of the absolute scale of influences, i.e. at different levels of the organism’s reactivity. In other words, a multi-level, periodically repeating structure of adaptation reactions was discovered.

It is known that the dialectical principle of periodicity is common to animate and inanimate nature. An example thereof is the periodic law detected by D.I. Mendeleev for chemical elements with different properties, which depend on the electronic configuration and atomic weight.

Another illustrative example is a periodic system of adaptation reactions, which represents a differentiated, biologically expedient system for selecting the organism’s response to a great variety of acting stimulating factors, both on the absolute scale (vertical), i.e. the reactivity levels, the so-called “floors”, and the relative scale (horizontal), i.e. the types of reactions [15].

It is just the existence of such a multi-level pattern of the adaption reactions, which provides for a flexible adaptability and which is an instrument to control homeostasis in different age periods of life. In childhood, the levels of reactivity are high, i.e. the “floors” are low,
and with age a person ascends the floors higher and higher, reducing the level of reactivity. Of course, we should strive for the reaction of youth and health. And the best of those reactions is activation, so the proposed novel therapy was given the very name: activation therapy.

Later on, the discoverers and their followers conducted a huge experimental and clinical research work on the development of strategy and fundamentals of the activation therapy.

Their new scientific approaches were based on the individualization of dose selection and the targeted formation of the necessary adaption reaction, the development of programmed dosage modes, the control of the state according to the signaling criteria of the reaction, and other fundamentally important aspects of the homeostasis regulation.

When translating research into the applied activation therapy, it has been necessary to dwell on the development of new methods for correction of neurohormonal and metabolic disorders, which appear during aging and tumor growth. It is known that there is a great deal in common between the methods of the correction, and consequently, between the activation therapy factors, too. During a long period of time the non-specific stimulation influences of varied quality and strength have been tested: from physical factors of electromagnetic nature (ultra-low frequency, ultra-high-frequency and optical ranges), neurotropic drugs (adrenalin, melipramine, etc.), molecular messengers regulating the hormonal, energy and proliferative potential (cAMP, ATP, succinic acid, ascorbigen, etc.), herbal and animal biostimulants (eleutherococcus, ginseng, leuzea carthamoides, aralia, pantohematogen, mumijo, etc.) up to reactively treated water.

Modern technologies for obtaining treated water, meeting specific requirements for limitations on concentrations of heavy isotopes of hydrogen, particularly, deuterium depleted water (DDW), lead to effects of changes in rates of biochemical reactions, restoration of intracellular, tissue- and system-related mechanisms of energetics, peroxidation and other metabolic processes [16-18]. This is reported by research sources from the USA, Japan, China and Russia.

When carrying out the DDW dosage activation therapy in animals, the following pronounced geroprotective effect was detected by us: with an increase in the occurrence rate of development and stable maintenance of the anti-stressor type reactions up to 100%, the effects of restoring the estrous cycle were observed.

That was an indirect factual evidence for the complex nature of positive changes in the organs belonging to the hypothalamic-pituitary-gonadal axis.

First of all, aging female rats in our trial studies differed in the hydrogen isotope deuterium content in their organs and blood. At the level of the whole organism, the stable maintenance of the anti-stressor reactions of training, calm and, especially, elevated activation produced effects on the appearance and motor activity of the animals. Besides, in experiments on aging rats with inoculated sarcoma 45, the use of DDW in combination with the experimental chemotherapy, showed an evident decrease in tumor volumes and accelerated tumor regression. It was verified by histological examination of the tumors in question and indicated the involvement of DDW in the formation of the non-specific anti-tumor resistance.

Thus, in our experiments carried out in aged animals, evidence for the possibility to activate the anti-aging and anti-carcinogenic effects produced by DDW on the organism as a non-specific component of the anti-stressor stimulation has been obtained.

So, it is just the ageing of the population in the world which is one of the causes of the growing cancer incidence rate.

The statistics data of 2015 show that the cancer incidence rate is the highest in the Western Pacific region - 32%; 26.4% are recorded for Europe and 3.8% for North Africa.

14 million cases of malignant neoplasms (MNP) have been found within the period of 1 year, including 8.2 million with a fatal termination. The prognosis is disappointing: by 2030 the cancer incidence might be expected in 21.7 million people, with 13 million mortality cases.

Adhering to the statistics, it should be noted that in the developed countries the number of cancer cases are significantly higher than in developing countries. Malignant neoplasms cause economic damages reaching hundreds of billions Dollars. The direct medical expenditures for the MNP treatment in the USA are evaluated to be 216 billion USD, and those in Europe amount to 75 billion EUR.

Since 1960, our Rostov Research Institute of Oncology has been developing and implementing most advanced technologies of the accompanying activation therapy used in cancer treatment [19-29]. Among the
activation therapy factors an important role is played by electromagnetic fields (EMF). This is a complex multi-parametric factor that requires an accurate selection of a frequency, an intensity and exposure. Variants of the applied EMF stimulation may be different: considered can be both the central exposure of the head, and the local exposure targeted at the tumor.

It is well known that the brain is a high-complexity built, multi-frequency, system. But we believe that a tumor is nothing but an oscillatory system with differing frequencies, which forms its own chaotically varying circuit. It has been evidenced by the specific EPR spectra of various tumor tissues demonstrated by Emanuel and Azhipa in the middle of the last century.

According to our engineering specifications, the Gradient-2 device was developed, a prototype of a large family of the medical devices with a wide frequency range: from ULF MF up to the optical region of the spectrum, as well as with scanning frequencies.

Firstly, we studied a wide range of intensity parameters. In our experiments on the model of inoculated and induced tumors, a complex nonlinear oscillatory dynamics of the antitumor effect in the range of the ULF MF intensity from 0.1 to 50 mT was revealed. In the said range, the periodically repeated optima of the MF intensity were determined, i.e. the regions of the range, where a pronounced anti-tumor effect, namely, growth inhibition and disappearance of malignant tumors in animals, was observed.

Then, using the model of chemical carcinogenesis, frequency algorithms, which included values close to the endogenous brain rhythms (0.03-0.3-3.0-9.0-12 Hz) were developed, and some mathematical patterns were used to vary the strength and time of exposure (exponential law, law of random numbers, etc.), allowing to observe the activation therapy principles. Actually, we have succeeded in development of a final R & D product best suited for introduction of the activation magnetotherapy into clinical practice.

Modern translational medicine offers new opportunities for using experimental developments in clinics. Of course, this is not a simple mechanical transfer or applications, but rather methods to be adapted to an individual. The technology of specific brain stimulation has been developed, and the conceptual principles of the correspondence of the frequency parameters, the exponential mode of delivery of intensity and exposure have been taken into account.

The use of activation magnetotherapy in the early postoperative period in patients with lung cancer improved the results if to compare with the case of the only surgical treatment. The total number of complications and the incidence rate of metastasis decreased, and the 3-year survival rate increased. The data confirmed the systemic anti-stress effect according to the indices of the brain cortical activity. Also, the regulatory effect of MF produced on the level of the hormonal and immune parameters was established.

In the treatment of lung cancer the preoperative chemotherapy is often used. We proposed a modification of neo-adjuvant chemotherapy, including exposure of blood to electromagnetic radiation of the optical range (the red region of the spectrum) before the cytostatics medication. The method allowed improving the conventional outcome and obtaining a clearly pronounced effect, which consisted in transferring patients from the inoperable to the operable state within a shorter period, reducing the number of CT courses from 2-3 to 1, and good CT tolerability due to reducing toxic effects.

A similar method was used for chemotherapy of breast cancer. The source of electromagnetic radiation was the Gradient-3 device. Inclusion of PCMT (Photo-Chromotherapy Method) into the treatment schedule improved the immediate anti-tumor effect and increased the adaptive potential of the organism and quality of life of the patients as compared with monochemotherapy.

It turned out that the application of PCMT as an independent therapy method had a pronounced positive effect in the treatment of complicated forms of hemangiomas in infants and young children. Without the use of radiotherapy, hormonal drugs and ointments, hemangiomas regression was achieved due to activated local mechanisms of vascular sclerosis, elevation of the immune status, development and maintenance of the integral adaption activation reaction.

The efficacy of the activation magnetotherapy as an accompanying factor in chemoradiotherapy has clearly manifested itself in patients with malignant brain tumors (astrocytomas, glioblastomas). The remission rate increased by 2.3 times, and the progression rate decreased by 7 times. Besides, the total and the disease-free 2-year survival rate significantly increased. These circumstances point to the need of expanding the clinical applications of the activation therapy technologies in health care practice.
Not only the central (to target at the brain), but also the local influence of specially selected modes of scanning MF can improve the results of the anti-tumor therapy. In this case, we are speaking about the experience obtained in onco-urology in the treatment of non-muscle invasive bladder cancer, which is characterized by a high rate of recurrence. Conducting courses of intravesicular chemotherapy with gemcitabine medication, with simultaneous exposures to SMF and PMF, has elevated the indicators of disease-free survival by 6 times. The first relapse in the reference group was recorded upon expiration of 6 months, and that in the main group of patients was identified after 18 months. Over the past 3.5 years of observation, relapses occurred in 36% of the reference group patients and only in 6% of those who received additional SMF stimulation treatment.

All the stated clinical and experimental examples of the effective anti-tumor treatment suggest the relevance and feasibility of development of methods for mobilization of protective forces and increase in the non-specific resistance by the organism.

In conclusion, it is necessary to emphasize that the formation and maintenance of stable anti-stress reactions in the organism is a necessary condition for prevention and treatment of any pathological process. For this purpose, a theoretical basis for the accompanying therapy of cancer and many other diseases, first of all, the cardiovascular, respiratory and digestive system diseases, neuro-endocrine and immune disorders has been created. The common conceptual ideas of the approaches to the study of stress and anti-stress reactions, despite the distances between countries and continents the researchers live in, contributed to the formation of a unified theory of the organism adaptation reactions as an effective, theoretically substantiated tool to control the organism state and its resistance. This discovery is a public property in possession of all people on the Earth, regardless of their age, sex and origin, and its scope may cover all spheres of life from sport to space exploration, hard work and sanatorium treatment.

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