

Methodological fundamentals of experimental magnetotherapy of tumors (historical essay)

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Abstract

The paper highlights the key stages on the way of a proper understanding of the magnetic field anti-tumor influence mechanisms on the level of an organism as an integrated system and its individual subsystems. The experiments in animals have shown that the processes of the malignant tumor growth inhibition are closely related to the formation of the stable state of the activation reaction at high reactivity levels. It is noted that the induction of such adaptational reaction depends on a specified selection of parameters of exposure intensities and magnetic field frequency, taking into account the law of nonlinearity of an exposure effect and adequacy with endogenous rhythms.

Keywords

Magnetic fields, Anti-tumor resistance, Adaptational reaction, Nonlinear effect, Biosystem synchronization, Activation therapy

Imprint

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In the present article given are results of many years' experience of magnetic field (MF) applications by the Rostov-on-Don Oncology Research Institute (RORI) experimental department. The material on the experimental studies is presented in a generalized form. Despite the fact that the studies were started more than 50 years ago, an assessment and an analysis of the MF effect on an organism and tumor process are carried out taking into account some modern conceptions of nonlinear interrelations between the complex bio-systems and the factors of the electromagnetic nature, the processes of their regulation and the mechanisms of communication of elec-

tromagnetic signal information value. Undoubtedly, the most topical is the issue of the mechanism of the MF anti-tumor effect with variations of its efficacy depending on biotropic parameters [1-7].

The methodological basis for the study of the MF anti-tumor action conducted by RORI is the theory of adaptational reactions (by Garkavi L.Kh., Kvakina E.B. and Ukolova M.A., 1975, 1977, 1979). The development of this theory is closely connected to magnetic biological studies not only due to history, but also due to experimental justification of some of the theoretical statements. The description of new, not known before, adaptational reactions of training

(Garkavi L.Kh., 1969; Ukolova M.A., Kvakina E.B. 1969) and activation (Garkavi L.Kh., 1968, 1969, 1977) determined an algorithm of a pioneering program for complex study of the CNS, the endocrine and thymus-lymphatic system, systems of connective tissue, energy exchange and a resistance level assessment under exposures of permanent and varying MF (PMF and VMF, respectively) [8-16].

A number of researchers confirm the prospects of studies on the magnetic effects, the alternative field in oncology. Thus, observed was a decline in the Ehrlich's adenocarcinoma inoculation in albino rats when exposed to permanent (PMF) or varied (VMF) magnetic field of a strength of 1500-1700 Oe (Lenzi M. 1940), rejection in some rats with I and II tumor generation under PMF of the 3000-4000 Oe strength, and retardation of growth of spontaneous tumors in rats' mammary glands under PMF exposure (Barrothy M. and J. 1963, Gross Z., 1964) [17-21]. The complete resorption of the experimental tumors and their replacement with connective tissue were for the first time reported by our colleagues M.A. Ukolova and G.G. Khimich (1960) who used magnetized rings, made of steel wire, which were fixed around the tumor contour (the S-45 and "novocaine and synoestrol" culture lines for rats). In 60% of the cases a resorption of the tumor of 1.0 to 1.5 cm in diameter was observed. The same effect was produced due to rotation of bar magnets of 500 Oe strength above the tumor. More pronounced MF control effect on the S-45 growth was obtained when combining the MF and ionizing radiation exposures (Kh.A. Komurdzhev, E.B. Kvakina, I.K. Meleshonok, S.A. Savina, 1967).

At the first stages of the development of pioneering methods of the MF control effect on the tumor growth, a local MF exposure prevailed. Further studies of efficacy of the magnetic field exposures showed the possibility of control effect on the tumor growth using the MF applied to the head of the animal-tumor bearer. That was based on data on high sensitivity of the CNS and especially the hypothalamus to the MF exposure (Y.A. Kholodov, 1966) and its

role in the tumor process (Zimel H. et.al, 1960, 1963; Lacassagne A., 1961; Kavetsky R. Y. 1962; Ukolova M.A. et.al., 1966) [22-28].

E.B. Kvakina's research (1972) showed that exposure with infra-low frequencies (ILF) (0.003-1.0 Hz) PMF of low intensity (10-50 mT) applied to the animal head leads to a retardation of growth of the inoculated and induced by chemical carcinogens tumors, located outside of the brain, up to their complete resorption in 40-60% of the cases. The PMF of the same strength increased the anti-tumor resistance only in case if the exposures started well in advance (2.5 months) before the tumor inoculation. What is the essence of the mechanism of the MF anti-tumor influence when the heads of rats-tumor bearers are under exposure? When studying the CNS functional state, E.B. Kvakina and her colleagues identified a dependence of its activity level on the value (strength) of the PMF and VMF biological effect. Under certain values of the VMF, the laboratory animals electrocorticogram demonstrates marked activation of EEG and the activation reaction development (increase in beta-like waves and decrease in gamma- and delta-waves) that indicates the prevalence of the process of excitation. At the same time, the animal motoric activity increases. Decrease in the exposure strength leads to the training reaction when some increase in the slow delta-waves quantity is observed as compared to the activation reaction. Thus, a certain interrelation between the exposure value and the CNS functioning level exists (Serebryakova L.A., 1976). According to G.Y. Chernyavskaya (1974), in the brain hypothalamic segment under the VMF exposure, leading to the tumor regression, a significant elevation of tissue gas exchange, oxidative phosphorylation and especially the capability to form high-energy compounds, aerobic and anaerobic glycolysis takes place. In the experiments by Y.S. Kotlyarevskaya (1974) obtained is the evidence of the changes in the brain hypothalamic segment functional state by the indicators of excitation and the resistance of a brain area between the electrodes, and the PMF effect differs from that of the

VMF exposure applied to that area. An elevation of the stimulation thresholds and a shift of the resistance dynamics (increase in the ohmic resistance and decrease in the capacitive one) as well as the adreno-negative action of the PMF characterizes it as a weak stimulus inducing the prevalence of the protective "preventive" inhibition in the brain. The VMF is responsible for the prevalence of the excitation processes in the CNS that is expressed in a decrease in the stimulation thresholds and a change in the brain resistance dynamics that is detected by the absence of the ohmic resistance increase and the capacitive resistance decrease as well as by the manifestation of the adreno- and cholino-positive action. This evidence demonstrates the VMF acts as a stimulus of the "middle" strength that causes the prevalence of a moderate excitation in the brain. At the same time, the change in microcirculation and glioneuronal relations with the neuroglia activation is observed in the hypothalamus (Kvakina E.B., Shibkova S.A., Isajanova S.Kh., 1974).

A correlation between the changes in the CNS, the endocrine glands, the thymicolymphatic system and connective tissue in case of the central exposure (applied to the head) by the VMF, leading to the tumor regression, with the alterations recorded by L.Kh. Garkavi (1964, 1968) at the middle strength of the hypothalamus electric stimulation and the middle-scale dosing of neurotropic substances allows identifying the activation reaction under the VMF exposure. Under the said PMF exposure, reported is development of the training reaction, as it is the case with a weak electric stimulation of the hypothalamus and low dosing of neurotropic substances.

The comparison studies of the MF exposure efficacy of the central (applied to the head) and the peripheral (applied to the tumor) exposures, carried out by G.Y. Maryanovskaya (1974), demonstrates the similarity of the physiological mechanisms of the anti-tumor resistance. The anti-tumor effect in both cases (81% - growth retardation and tumor regression under the MF exposure applied to the head in total, 73.8%

- under exposure applied to the tumor) is observed only in case of implementation of the complex changes typical for the unspecific reactions of training and especially activation. Biophysical studies show that the one of the primary mechanisms of the MF influence on the organism is an action on free radicals having high magnetic sensitivity and participating in the basic physiological and biochemical processes in the organism. Thus, it is detected with the method of the electron paramagnetic resonance (EPR) that the VMF exposure changes the free radicals content both in the organism and in vitro in the blood-ascorbic acid model system. An increase in the free radicals level in the organism (when injecting the radical forming agents) leads to an enhancement of the MF anti-tumor activity.

The most important part of the MF anti-tumor exposure mechanism is represented by the processes, which determine the state of the tumor itself, i.e. the local reactions. The examinations of the tumor cell histo- and ultrastructures after the MF exposure demonstrate destructive changes in cell membranes and nuclei, disorder in the synthetic activity and energetic deficit in cells, buildup of dystrophy, necrosis, i.e. the progression of irreversible changes in the tumor tissue (the evidence is obtained by L.S. Ogorodnikova together with N.G. Gairabedyants). These changes in the tumor during its regression are close in character to the phenomena of suppression and depletion under the stress, the capability of which to develop at the cellular level is well-known (Kalendro G.S., 1972). It has been also demonstrated that the spread of the tumor process under ineffective MF exposures leads to the stress aggravation and the organism anti-tumor resistance suppression, while the local tumor tissue reaction is of over-activation type (Kuryshv I.Y., 1985).

An applicable dialectical interpretation of the interrelations between the general reaction in the organism and the local reaction in the tumor allows identifying a possible option of a targeted influence both on the processes and developing the methods of how to control them. Strong evidence of decrease in dama-

ging effect of chemotherapy and radiation (experiments by F.M. Zakharyuta) demonstrates the outlooks for the MF application as a factor capable of managing and modulating the anti-tumor influence of the chemo- and radiation therapy. The development of the training and activation reactions under the PMF and VMF exposures results in a decrease in lethality rate and leucopenia, an activation of the lymphoid cells in the thymus and the lymph nodes, an increase in the anti-tumor effect in the animal-tumor bearers which were subjected to treatment with alkylating agents or radiation. The practical value of these studies is determined not only by the MF exposure optimization capability, but also by its power to suppress the tumor cell proliferative activity using medication doses lower than the therapeutic ones (Zakharyuta F.M., 1989). One of the most informative markers of the state of the local and general reactions in an organism is an identification of the presence of sulfhydryl groups, the reactivity of which allows evaluating the level of the organism resistance and the adequacy of the applied MF exposures in combination with chemo- and radiation therapy.

However, for an identification of the general unspecific adaptational reaction in the organism, a simpler and a more convenient marker (the morphological structure of white blood cells) capable of assessing the nature of the changes in progress in 6-24 hours upon exposure (Garkavi L.Kh., Kvakina E.B., Ukolova M.A., 1974, 1975) has been proposed. The application of a leukogram as an integral reaction signal test provides the realization of one of the main principles of the activation therapy that is similar to the cybernetic principle of feedback and that makes possible to adjust the required signal value at the systems "input" and thereby regulating the response at the "output" of the system. Thus, the proper understanding of the quantitative and qualitative relations between the "quantity" of the exposure and the "quality" of the response in the presence of the signal marker of the feedback provides the basis for the intended targeted application of the magnetic therapy under clinical conditions.

At the first stage, the MF influence on the tumor was studied according to visual localization of the processes. Clinical investigations on large-scale material showed the capability of obtaining a complete resorption of the lower lip and skin tumors (R.N. Salatov) with favorable outcomes after the MF exposure completion. Basing on the evidence, a pioneering method for malignant tumor treatment was developed (Patent No. 522688, USSR, 1974). The patent claim consists in the local sinusoidal MF (in intermittent mode) exposure applied to an affected area, distinguished by the fact that it is conducted under the activation reaction control to reduce treatment time and individualize the exposure regime. In the treatment process, an observation on the changes in the blood picture is carried out; a decrease in segmented neutrophils, an increase in lymphocytes number, dystrophic processes in the tumor, connective tissue growth, and a lymphocytic reaction are noted. Besides, in the study of the MF local exposure in the magnetic therapy, full safety of the proposed treatment method has been confirmed and the absence of contraindications thereto has been established.

Further fundamental studies of the MF exposure as a high-effective biological factor influencing the organism reactivity led to gaining a more penetrating insight into the fundamentals of the organism adaptational performance.

It has been demonstrated that the three adaptational reactions (training, activation, stress) are not the only capability of an organism to provide responses to MF exposures of various biological intensity. In literature described are some biological effects produced by MF in wide ranges of its intensity, from a fraction to tens of thousands of mT, with varying time of exposures from a second up to many months. But with all the variety of changes in the organism, there is no simple linear dependence available, namely, a rise in the effect with increasing the MF "dose". Sometimes weak field exposures are capable of producing an even more intense effect than it is the case with the strong ones (Presman A.S, 1968; Muzalevskaya N.I., Larkina T.A., 1974), and reported are

also the availability of the same changes detected under different exposure intensities (Gorshenina T.I., Frumkis A.E., 1974).

A hypothesis has been proposed considering a possible development of the adaptational reactions of the same name to MF exposure, differing in their absolute values, in a wide range of intensities. In other words, assumed is the existence of a certain periodical repeatability (cyclicity) of the reactions tetrad as the stimulus strength increases or decreases (Garkavi L.Kh., Kvakina E.B., 1975; Kvakina E.B., Garkavi L.Kh., 1975). The hypothesis was verified by experiments in albino rats (more than 750 animals), the cohort of which was used for studies of the biological action of the MF with the 0.1 to 50 mT intensity, the 50 Hz frequency in an intermittent mode provided by the "Polyus" device designed by VNIIMP (for experimental studies by A.I. Shikhlyarova). The type of the developing of the adaptational reaction was identified according to the hemogram, the number of leukocytes, the thymus weight and the correlation between the gluco- and mineralocorticoid adrenal cortex hormones. According to the obtained results, the reactions of training, calm and elevated activation and stress have been reported to be reproducible within the studied range of the MF intensity.

An in-depth analysis of the obtained experimental material and a generalization of the data from literature sources allowed developing a new concept of multi-level periodic system of the organism reactions to influences of external environment factors in a wide range of strength (dose) (Garkavi L. Kh., Kvakina E.B., 1975 – 1990; Kvakina E.B., Garkavi L. Kh., 1975). According to the concept, provided that an organism is considered as an integrated system, the periodicity of the reactions tetrad is closely linked to the several levels of reactivity ("the number of the floors"). On each level, the clear-cut quantitative and qualitative relations are identified: the stimuli to be treated weak for a given level induce the training reaction; the middle-scale stimuli cause the calm reaction and the elevated activation reaction, and the strong stimuli are re-

sponsible for development of stress. An application of the stimuli exceeding an intensity value, being the greatest (stress) for a given range, leads to passing to the next range. Thus, we may say that in case of multi-level homeostasis regulation the organism utilizes two reference systems: the relative reference system and the absolute one. An absolute value of a stimulus determines the level of the reactivity the response develops on, and the response type is identified according to the reference strength scale: the stimuli which are weak for a given level cause the training reaction, the middle-scale stimuli induce the calm reaction and the elevated activation reaction, and the strong stimuli give rise to stress. Since the previously obtained evidence demonstrated the best increase in the anti-tumor resistance in case of development of the activation (especially elevated) reaction, it was of great interest to conduct a comparative study on the anti-tumor efficacy of MF exposures with variable intensities, causing the activation reaction on different levels of the reactivity. In experiments by A. I. Shikhlyarova, conducted in rats with tumors of different etiology (inoculated sarcoma line, chemical carcinogenesis, hormone dependent ovarian tumors), applied was VMF within the intensity range from 0,1 to 30,0 mT with standard parameters (frequency: 50 Hz, exposure time: 2 min., current waveform: sinusoidal, mode: intermittent). The results of an assessment of the tumors volume, percentage of regression, growth retardation and the data on the tumor histological examination have demonstrated the non-linear change in the anti-tumor effect. Graphically it is expressed as a wave-type curve, the maxima of which correspond to 0,1, 0,7, 3,2 and 35 mT, and the minima refer to 1,4, 8, 30 mT, respectively. The best anti-tumor effect (40% of the cases of full tumor regression in short periods) was observed under a VMF intensity of 0.1 to 3.2 mT. The study of the complex of the adaptational reaction markers has detected that the VMF anti-tumor influence of different intensity is based on the mechanism of the activation reaction development. Besides, an application of the activation reactions of high levels of reactivity is preferable as it contributes to an increase in the VMF influence efficacy and shortens the period of treatment (Shikhlyarova A. I.,

1975). Even greater efficacy of the training and activation reactions caused by the MF low intensity has been demonstrated in a combined treatment with chemotherapy (researches by F. M. Zakharyuta, G. V. Zhukova, E. A. Sheiko).

For humans received the above mentioned pioneering therapy, the said regularity was fully confirmed both by the clinical evaluation of the MF treatment efficacy and the markers characterizing the developing reactions: leukogram, biochemical analysis of the thyroid gland and the data on adrenal cortex hormone content in blood.

The identified dependence of the electromagnetic influence efficacy on EMF strength (intensity) does not exclude, but, on the contrary, denotes that it is necessary to study biological efficacy of other biotropic parameters of MF, including frequencies of the latter. According to the modern conceptions, a frequency determines a special form of the MF exposure, realizing the mechanism of communication of electromagnetic signal information value (Kaznatcheev V. I., Mikhailova L. P., 1985). Thus, an application of the electromagnetic fields (EMP) of infra-low and low frequencies has revealed the capability of biosystems to adjust to an external setting rhythm frequency if the difference in the frequency of the auto-oscillation system is of minor nature.

It has been proposed (Garkavi L.Kh., Kvakina E.B., 1985) that the basis of a response by an organism to an influence of EMP at various frequencies is just the system of discrete states, i.e. the tetrad of reactions (training, calm and elevated activation, stress) with the frequency characteristics typical for each of the reactions. The studies have demonstrated that in case of single weak low-frequency EMP exposures of intact animals with different initial states the reaction of the same type is formed under involvement of a certain frequency. Experiments by L.P. Barsukova have shown that with an increase in the EMP frequency observed is an effect of successive transition from one reaction to another (training-activation-stress) similar to what happens when building up the VMF intensity. These facts suggest that there is the existence of a mechanism responsible for converting a frequency (external setting rhythm) into a strength (measure of action) and vice versa (Garkavi L.Kh.,

Kvakina E.B., 1985). As a result of interrelations between the internal and external rhythms in a bio-system, we obtain a synchronization of the processes contributing to the integration of the biological system, i.e. providing its integrity and stability (Bartalanfi L., 1973; Blekhman M.I., 1971; Putilov A.A. 1987).

From the theoretical principles of activation theory, development of the activation reaction, determining the processes of rapid mobilization of energetic and plastic trophic resources, may be characterized as an optimally synchronized state of all the subsystems in an organism. This statement is supported by a high level of the processes coordination by the CNS (inhibition and excitation, with a slight prevalence of the latter), the endocrine system (balanced increase in endocrine glands functional activity without any elements of suppression) and the thymicolymphatic system (hyperplastic – within the norm – lymphoid tissue reaction). Even in the peripheral systems (skin, striated muscle complex, blood) in the organism, the activation reaction, synchronizing influence caused by MF exposure, is clearly manifested. Thus, A.K. Mulatova succeeded in detecting an increase in the functional activity of peripheral nervous formations. While under stress detected are signs of over-stimulation up to destruction of nervous elements in the skin and the muscles, and under the training reaction identified is a moderate impregnation of nerve fibers and endings, under the activation reaction caused by VMF observed are an increase in the number of the detectable nervous formations, an intensification of impregnation of the nerve fibers and beaded nodes along the nerve fibers in the form of neuroplasm leaks.

Owing to the desynchronization of the processes and deep disorders in activity of the main homeostatic systems in an organism under the tumor growth conditions, considered has been a possibility of homeostatic correction using weak EMP of not one specified frequency, but of a complete program of frequencies, including a successive set of frequencies of accord-arpeggio type and different structural sublevels (subcellular, cellular, tissue), close to their own natural oscillation frequencies (endogenous biological rhythms). Composing such program of the EMP exposures has achieved the main goal, namely, to provide

synchronization of the processes on the integrated organism level and an identification of the bio-system control perspective in case of tumor development (Shikhlyarova A.I., 2001).

Preliminary experiments in animals without tumors detected significant capabilities of the homeostatic correction in case of the EMP of weak intensity (0.1 – 1.0 mT) within the programmed frequency modes (0.03, 0.3, 3.0, 9.0, 50, 150, 450 Hz). Noted was a significant increase in the trophic and plastic potential of the thymicolymphatic system balanced with physiological strengthening of the endocrine glands activity. The results of the experiments in 150 rats-tumor bearers (with the inoculated S-45) demonstrated the possibility of a long-term maintenance of the normal total number of the leukocytes and the leukogram, the normal biogenic amine content in blood and adrenals, the normal immunological markers and the normal energy exchange in the liver and the brain in laboratory rats in comparison with the reference cohort data. It has been reported that the main resulting factor of efficacy of the EMP frequency modes is significant retardation of growth and regression of the tumors. The tumor volumes in the reference group have been recorded to be 2.0-2.5 times higher than the same in the experimental groups subjected to the proposed exposure treatment.

A significant increase in the anti-tumor effect, namely, regression of the tumors in 80% of the cases, was noted, when combining the EMP exposure with the cytostatic injections that demonstrated the modulating influence of the frequency signals on chemical agents injected (Shikhlyarova A.I., Garkavi L.Kh., Kvakina E.B., Barsukova L. P., 1990). Thus, the conducted studies allow evaluating the influence of the accord of the EMP frequencies, adequate to the various organism sublevels oscillation frequencies, as a factor responsible for synchronization of the processes, increasing the system stability in case of the tumor development. The prospects for such studies for maintaining and strengthening the bio-system space-time-related interconnections in the anti-tumor protection management is evident, since the studies may contribute to directing external field exposures in concordance with the evaluation of the main

parts of the nervous system, the endocrine and immune systems state for the purpose of their correction.

Actually, obtained are the evidences for the regulation, the harmonization and the anti-stressor nature of the processes of unspecific anti-tumor resistance increase under the ultra-low frequency magnetic field exposures, namely, re-arranging of energetic, free radical and synthetic processes, an activation of cellular and humoral mechanisms of the immune system, synchronization of the endocrine system activity and restorative morphofunctional transformations in the brain [29].

To summarize the above, we can conclude that starting with consideration of the complete scope of research on the MF anti-tumor phenomenon, revealing the MF exposure mechanism on the level of general adaptational reactions and identifying the law of periodicity of these reactions on different reactivity levels, studying the electromagnetic exposure anti-tumor efficacy scale and ending with the modern investigations of exo- and endogenic field interrelations, based on the intrinsic biological rhythms and the synchronization, the essence of our pioneering theory is associated with obtaining of more knowledge of the organism adaptational activity and the potential possibilities to control it. The above theoretical and practical experience creates a good foundation for a wide application of the MF exposure as an independent or an additional option in an effective treatment in oncology.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

A.I.S., G.Y.M., L.P.B., F.M.Z., G.V.Z., Y.P.K. carried out the experiments and analyzed the data. T.P.P., Y.A.S., O.F.E., T.A.B., T.A.K., N.M.M. contributed to the writing of the manuscript. A.I.S. coordinated and helped to draft the manuscript. All authors read the ICMJE criteria for authorship and approved the final manuscript.

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