PERTURBATION OF ENZYMATIC ACTIVITY OF THE HeLa NEOPLASTIC CELLS BY CYTOSTATIC ACTIVE ELECTROMAGNETIC TREATMENTS

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Abstract: The study of interactions of low frequency and intensity electromagnetic fields (100 Hz and 5.5 mT of LFI-EMF) with some membrane bound and intracellular enzymatic biomolecules of HeLa cells has revealed an enhancement of membranary Na^+-K^+-ATP-ase, intracell LDH, SOD and ALP activities, as well as a repression of cellular ATP-ase, CAT, ACP activities in the case of cEMF treatment. Moreover, dcEMF has intensified the enzymatic activity of cellular ATP-ase, Px, CAT, has accentuated MDA levels and has also reduced the functioning degree of membranary Na^+-K^+-ATP-ase and of intracellular LDH, SOD and ALP. In the case of Px, GSH-Px and lipid peroxidation interference with both EMF variants, we assist to the induction of a stimulator effect upon their activities. The different sense and amplitude of reactivity of neoplastic cells enzymatic systems to the electromagnetic field irradiation were dependent on the EMF application mode (continuous or discontinuous). These variations of the enzymatic activities could be due to a direct or indirect interaction of exogenous cEMF or dcEMF with cellular (plasmalemma) or subcellular (organelles) structures and intracellular biomolecules (enzymes, DNA, RNA etc.), as well as a summation of the exogen and endogen electromagnetic fields effects. Thus, EMF induces a significant cytostatic effect either by alteration of the HeLa cells membranary or metabolic processes, or by intracellular increased generation of free radicals.

INTRODUCTION

At present, the electromagnetic field, especially the one of low frequency and intensity, has become an ubiquitary presence in our live environment, being generated from the aerial wires to the appliances existing in our houses. Although it is a constant environmental factor, we know very little about its influence upon the physiology of the normal or abnormal cells and of the entire organisms.

Now, the *in vivo* or *in vitro* effects of the low frequency and intensity electromagnetic fields aren’t totally known, unanimously accepted and discussed from the point of view of their probable action mechanism. This fact is caused by the great number of experimental data mentioned in the bioelectromagnetic and bioelectromagnetism specialty literature and by their contradictory and heterogeneous aspects.

The known effects of the LFI – EMF fields can be divided in: positive (with neurological, endocrinological, immunological, hematological, locomotor expression) and negative (as fertility diminution, memory deficiency, growth and development disorders, involvement in the carcinogenetic process), without the elucidation of the cellular, subcellular or molecular substratum with which the electromagnetic field interacts in determination of these effects ((Jitariu, 1987; Ailiesei, 1996; Wartenberg, 2001; Karasek &Lerchl, 2002; Teodori et al., 2002a; Teodori et al., 2002b; Chionna et al., 2003; Rosen, 2003; Tofani et al., 2003; Abbro et al., 2004; Assunção Guimarães &Linden, 2004; Marinelli et al., 2004; Moreira &Barcinski, 2004; Chionna et al., 2005; Dini &Abbro, 2005; Pagliara et al., 2005; Tarantino et al., 2005; Tenuzzo et al., 2006). The heterogeneity of biological responses to the action of the electromagentic fields traces a very thin demarcation line between the positive and negative ones, many controversies appearing nowadays upon the “real” character of the EMF biological effects.

Nevertheless, the reactivity of some cytophysiological processes of the healthy animal cells and its capitalization in different therapeutic purposes – especially in the locomotory disorders (Jitariu, 1987; Ailiesei, 1996; Zamfirescu et al., 2000) – suggested to us the utility and importance of a complex research on the interaction between the low frequency and intensity electromagnetic fields and the neoplastic cells, in obtaining the scientific basis adequate to conceive some new and efficient antineoplastic therapeutic strategies.

Thus, the first lines of research (Rotinberg et al., 2007; Mihai et al., 2008) have highlighted the *in vitro* reactivity of some membranary and metabolic processes, as well as the modifications in the respiratory pattern of the HeLa neoplastic cells, to the action of EMFs (100 Hz, 5.5 mT), applied continuously or discontinuously. The main alterations of the HeLa cells cytophysiological profile were: the perturbation of the ionic transmembranary fluxes and of extracell/intracell ionic ratios, the intensifications of the glycogenogenesis, lipogenesis and proteinosynthesis; the stimulation or inhibition of the nucleic acids biosynthesis; the attenuation of the cholesterolgenesis; the enhancement of the intracellular metabolic utilization of the glucose, lactic acid, free fatty acids and aminoacids biomolecules as anabolic

sources and fuel resources, the stimulation of the cell respiration and energetics, revealed by the high levels of the oxygen consumption and by the ascendant route of great amplitude of the respiratory dynamics,

These specific membranary, metabolic and energetic profiles of HeLa neoplastic cells, submitted to the EMFs action – which characterize a cytostatic impact – can be the consequence of the primary interaction of the EMFs either with the plasmatic membrane or with cellular, subcellular and molecular structures (from nucleus, organelles, DNA, RNA and enzymatic biomolecules) which modifies the gene pattern expression, the oxygen free radicals production as well as the activity of some metabolic key enzymes (Brüne, 2003; Chionna et al., 2003; Marinelli et al., 2004; Stevens, 2004; Chionna et al., 2005; Dini &Abbro, 2005; Tenuzzo et al., 2006).

No matter the cellular level of the primary interaction mechanism, the low frequency and intensity electromagnetic fields have induced obvious, significant and indubitable modifications of some membranary and metabolic processes, which perturb "the new" steady-state of the tumoral cell, suggesting even an own cytostatic property, dependent on the electromagnetic field type.

Consequently, we have decided, in the present paper, to follow the interference of low frequency and intensity electromagnetic fields with membrane and intracellular enzymatic biomolecules of the neoplastic cells and their activities implicated in the cellular metabolism or in response to the oxidative stress. The bulk of results which will be achieved in this experimental frame, on adequate in vitro experimental models, will represent a new piece of evidence regarding the possible action mechanism implied in the expression of cytostatic effect of low frequency and intensity electromagnetic fields.

MATERIAL AND METHODS

The biological material used in the *in vitro* experiments was represented by mycoplasm-negative, stabilized, HeLa cellular cultures of human neoplastic origin, obtained from an uterine cervix carcinosarcoma and cultured in DMEM growing medium (Dulbeco's Modified Eagle's Medium, Biochrom AG, Germany, FG 0415), supplemented with 10.0% fetal bovine serum (Sigma, Germany, F9665), 100 µg/mL streptomycin (Biochrom AG, Germany,A 331- 26), 100 IU/mL penicillin (Biochrom AG, Germany, A 321-44) and 50 µg/mL antimycotic amphotericin B (Biochrom AG, Germany, A 2612), at a density of 2×10^6 cells / 300 cm^2 flask, in a humidified 5% CO_2 atmosphere at 37°C. [ ]. The cells were incubated for a period of 144 hours**,** the growing medium was renewed twice in this time frame of cultures development. When the cells reached confluence in the monolayer stage, the cultures were divided into control and electromagnetic treated cell cultures.

The electromagnetic fields (EMFs) of continuous or discontinuous type (cEMF, dcEMF) were generated by an IBF magnetodiaflux device. This presents two circular coils (29 cm in diameter, placed at a distance of 14.5 cm) disposed on a cardboard cylinder, which delimit inside a precinct arranged for the placing of the culture flasks during the electromagnetic treatment. The intensity and frequency of the generated electromagnetic field were of 5.5 mT and 100 Hz, these parameters including it in the category of the low frequency and intensity electromagnetic fields.

Single EMF was applied continuously or discontinuously (with breaks of 1 second and action 3 seconds) to the 144 hours "treated" cell cultures, for a period up to 60 minutes. Simultaneous experiments skipping the electromagnetic field were also performed on the control cultures. During the real or blind treatment the cell cultures were removed from the incubator in the magnetodiaflux precinct, where the temperature reaches up to 30°C.

At the end of this short term *in vitro* electromagnetic treatment (60 minutes), the medium was discarded from the test flasks. The layer of tumoral cells was washed with phosphate buffered saline, precisely weighted and then subjected to the steps of obtaining the clarified cellular lysates. Adequate aliquots were used for the biochemical determination of the membranary Na^+-K^+-ATP-ase, cell Mg^{2+}-ATP-ase, lactat dehydrogenase (LDH), peroxidase (Px), gluthation-peroxidase (GSH-Px), superoxid dismutase (SOD), catalase (CAT), acid (ACP) and alkaline (ALP) phosphatase activities and of malondialdehyde levels (MDA) (Artenie et al., 2008).

The estimation of the total Mg^{2+}- Na^+ - K^+ and respectively membranary Na^+-K^+-ATP-ase (tATP and mATP) activities, expressed in mg inorganic phosphate/minute/g cellular mass (mg Pi/min/gcm) was based on the amount of inorganic phosphorous released after ATP hydrolysation by ATP-ases present in the cellular homogenate. Lactate dehydrogenase activity (µM/min/gcm) was determined through the measurement of NADH oxidation velocity in the case of transformation reaction of pyruvic acid in lactic acid. Peroxidase activity (peroxidase unit, UP, /min/gcm) was estimated by orto-dianisidine method, which measures the intensity of the o-dianisidine oxidation product colour.

Glutathione peroxidase activity (µM GSH/ml/min/gcm) was measured on the basis of the reaction of unconsumed reduced glutathione with 2, 2'- dinitro-5,5'- dithio-dibenzoic acid (Merck), which drives to a yellow, photometrable complex.

The evaluation of superoxid dismutase activity (superoxid dismutase unit, USOD, /ml/min/gcm) is based on the enzyme capacity to inhibit the nitroblue tetrazolium reduction by the superoxid radicals generated in reaction medium through riboflavin reduction.

Catalase activity was estimated through spectophotometric registration of the hydrogen peroxide consumed quantity, being expressed in enzymatic unit (UE/gcm).

Alkaline and acid phosphatases activities (international unit,U.I.,/gcm) were determined with para-nitrophenol, which is converted in a spectrophotometrable product, p-nitrophenolat, under the action of phosphatases.

At higt temperature and in acid medium, malondialdehyde – product of lipid peroxides degradation – reacts with 2-thiobarbituric acid, leading to a photometrable pink trimetinic adduct (MDA nM/ml /gcm).

Five flasks of cultures have been used for each experimental group, the results being analyzed statistically by means of Student’ „t” test (Cann, 2002).

RESULTS AND DISCUSSIONS

The investigation of the consequences of the cytostatic electromagnetic treatment (applied continuously or discontinuously) upon HeLa cell cultures has conducted to a set of data – shown in figure 1 and 2 – which expresses this physical agent's modulation of some cellular enzymatic activities. Thus, the action of exogenous electromagnetic energy upon the activity of different enzymatic systems has materialized, comparatively with the one of the control group, through variations of its sense and amplitude.

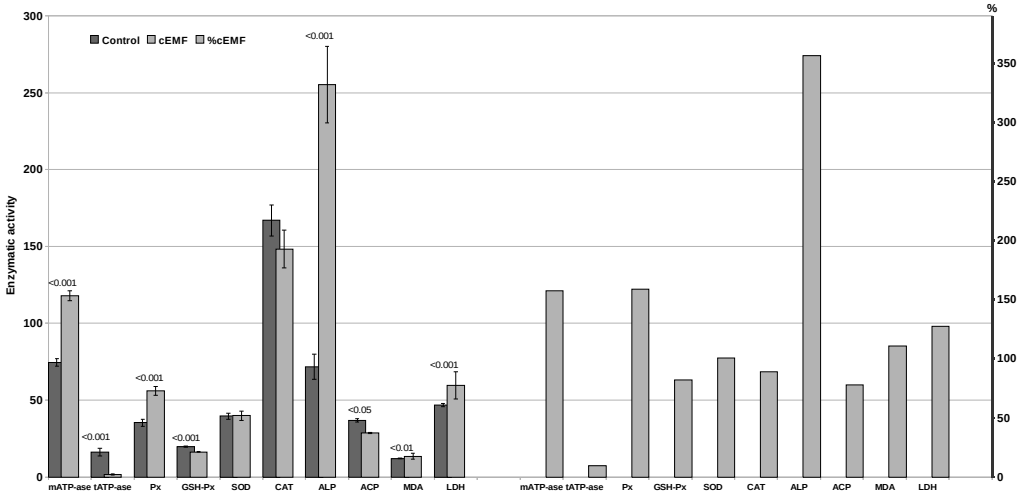

Fig.1. Modulation of the membranary Na^+-K^+-ATP-ase (mg Pi/min/g cell mass), cellular Mg^{2+}-ATP-ase (mg Pi/min/g cell mass), LDH (µM/min); Px(UP/g/min.); GSH-Px(µM GSH/ml/min.); SOD (USOD/ml/min); CAT (UE); ACP(U.I.); ALP(U.I.) enzyme activities and MDA levels (nM/ml) of HeLa cell cultures caused by the continuous electromagnetic treatment (100 Hz/ 5.5 mT/ 60 min.).

It can be seen, from both figures, that in the case of the control HeLa cell cultures, enzymatic activities were of: for membrane Na^+-K^+-ATP-ase, 74,7 mg Pi/min/gcm; in the case of cellular Mg^{2+}-ATP-ase, 16.15 mg Pi/min/g cm; for LDH, 46.7 µM/min/gcm; in the case of Px 35.28 UP/gcm/min.; for GSH-Px, 19.86 µM GSH/ml/min/gcm; in the case of SOD, 39.6 USOD/ml/min/gcm; for CAT, 166.89 UE/gcm; in the case of ACP 36.90 U.I./gcm; for ALP 71.66 U.I./gcm; in the case of lipooxidation enzymes, 12.10 nM MDA /ml /gcm, us considering these quantitative estimations as reference values, necessary for the interpretation of the EMF's impact signification upon the activity of the studied enzymes.

As compared to the control group, the interference of electromagnetic field, applied continuously, with enzymatic activities has determined significant functional and statistical modifications of these membranary and intracellular biomolecules (Fig. 1). Thus, the activity of membranary Na^+-K^+-ATP-ase has been amplified with 57.7%, while the functioning level of cellular Mg^{2+}-ATP-ase has been repressed with 90.3%. In the case of the enzymes implied in the response to oxidative stress, we assist to an enhancement of some activities with 58.7% (Px), 0.76% (SOD), and 10.7% (MDA), respectively, or attenuation of some functionality with 18.0% (GSH-Px) and 11.1% (CAT), respectively. The activity of lactate dehydrogenase was intensified with 27.6%. It can be also observed that the ALP and ACP are modulated, the activity of the first registering an augmentation (with 256.2%) and the second's revealing a regression (with 22.2%).

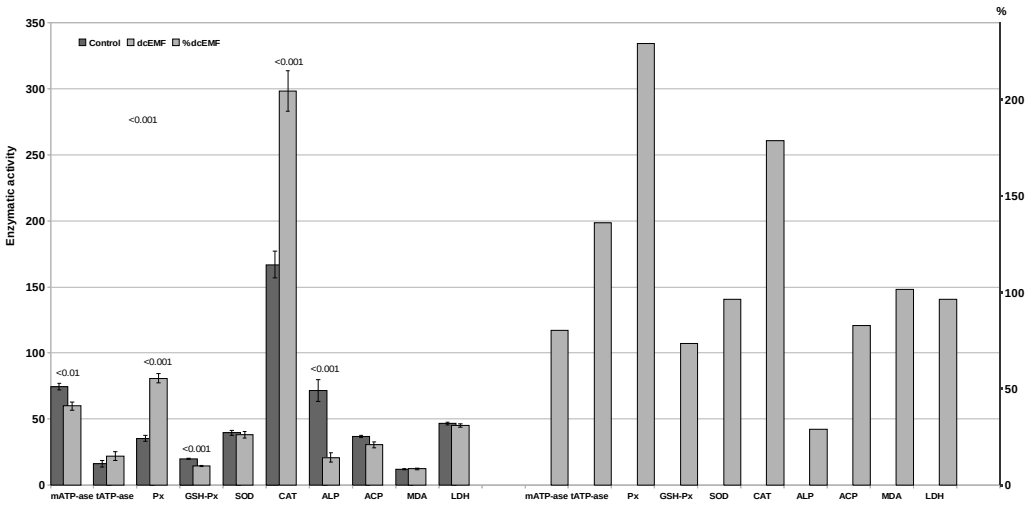

Fig. 2 The impact of dcEMF (100 Hz, 5.5 mT, 60 min.) upon the activities of membranary Na^+-K^+-ATP-ase (mg Pi/min/g cell mass), cellular Mg^{2+}-ATP-ase (mg Pi/min/g cell mass), LDH (µM/min); Px(UP/g/min.); GSH-Px(µM GSH/ml/min.); SOD (USOD/ml/min); CAT (UE); ACP(U.I.); ALP(U.I.) enzymes and upon MDA levels (nM/ml) of HeLa neoplastic cells.

In comparison with the control enzyme activities, the impact of discontinuous EMF upon the HeLa cells has materialized by intensification or repression of the enzyme activities (see Fig. 2). The total ATP-ase functioning level was enhanced with 36.13%, while membranary Na^+-K^+-ATP-ase activity was repressed with 19.60%. The activity degrees of peroxidase and catalase were amplified with 129.20% and 78.74%, respectively. In the case of GSH-Px, ALP and ACP a reduction of their activities has been highlighted by 26.6%, 70.9% and 17.1%, respectively. Finally, the SOD and LDH activities, as well as the lipid peroxidation were negligibly inhibited or stimulated by the discontinuous electromagnetic treatment.

Generally speaking, we can emphasize some differences of the neoplastic cells enzyme reactivity to the low frequency and intensity electromagnetic field action, their sense and amplitude being dependent on the way the EMF is applied, whether continuous or discontinuous. Both cEMF and dcEMF have induced a clear intensification of some enzymatic activities. Thus, membranary Na^+-K^+-ATP-ase, LDH, Px, GSH-Px, SOD and ALP activities, as well as the lipid

peroxidation were amplified by cEMF, while total ATP-ase, Px, CAT and lipid peroxidation were enhanced by dcEMF. On the other hand, cEMF has diminished the activity of total ATP-ase, CAT, ACP, while dcEMF has repressed the function of membranary Na^+-K^+-ATP-ase, of LDH, SOD and ALP.

Our experimental results, registered after an unique short lasting treatment of HeLa cells with continuous or discontinous electromagnetic field have highlighted an increase (in the continuous electromagnetic application) and a decrease (in the discontinuous electromagnetic application) of the inorganic phosphate, in the membrane and intracellular substratum. These quantitative variations have suggested either a high activity of the membrane Na^+-K^+ electrogenic pump and of the total ATP-ases, in the case of continuous electromagnetic field action, or a low activity of these enzymes in the case of discontinuous EMF action. Thus, we assist to a modulation of the cell ATP–ases system activity, comparatively to the one of control. Therefore, we have appreciated that the continuous electromagnetic field has a stimulatory impact upon the activity of this enzyme system and the discontinuous electromagnetic field has an inhibitory impact upon the membrane Na^+-K^+-ATP-ase activity.

The different degrees of membrane Na^+-K^+-ATP-ase activity reveal diverse energetically needs for the insurance of the optimal active transmembranary fluxes of Na^+ and K^+ cations in the electromagnetically treated HeLa cells.

The stimulatory and respectively inhibitory effect of the continuous and respectively discontinuous electromagnetic field upon Na^+-K^+ membrane electrogenic pump can be the consequence either of a direct interaction of the electromagnetic fields with some membrane structures, or of the preliminary binding of the electromagnetic energy with the membrane Na^+-K^+-ATP-ase biomolecule, this enzyme being itself the target of the EMF action. Our assumption is according to some recent bibliographical information (Teodori et al., 2002a; Teodori et al., 2002b; Rosen, 2003; Tofani et al., 2003; Marinelli et al., 2004; Dini &Abbro, 2005; Tenuzzo et al., 2006), which suggest that the plasma membrane is the site of its primary action. The short lasting *in vitro* electromagnetic treatment of the HeLa tumoral human cells modulates the membranary Na^+–K^+–ATP-ase and total ATP-ase activities and, inherently, alters the membrane permeability, transmembranary ionic fluxes, ionic equilibrium, extra- and intracellular ionic ratios.

Consequently, EMFs will modify both optimal conditions for the diverse intracellular enzymatic systems’ activity and the unfolding of the metabolic events. In relation to this hypothesis, the research was focused on the effect of EMF exposure upon several enzyme biomolecules.

A key-enzyme of the glucidic intermediary metabolism and a well-known marker of malignant cells is lactate dehydrogenase, which was also submitted to electromagnetic energy by the HeLa cells irradiation with continuous and discontinuous EMFs. In the conditions of the cytostatic electromagnetic treatment, the LDH activity was obviously perturbed by EMF exposure, especially by the cEMF. Its activity was characterized by a tendency to intensify, probably due to reduction of pyruvate or NAD^+ synthesis.

Another remarkable and significant enzymatic system, implied in the phosphorilation and dephosphorilation cell metabolic reactions, includes the ALP and ACP phosphatases, their behavior to the electromagnetic irradiation highlighting a different reactive profile related to the EMF type. In our experimental conditions, the cEMF has excessively stimulated the ALP activity and has correspondingly inhibited the ACP one. Further, the localization of the ALP enzyme at membrane level can facilitates its interaction with the electromagnetic energy, in the conditions

of the HeLa cells exposure to the action EMFs, especially cEMFs. Contrary, ALP activity was significantly repressed under the dcEMF treatment, which probably generated an increased intracellular production of the cytotoxic free radicals.

The above mentioned supposition is also argued by our experimental results regarding the functional behaviour of the free radicals scavenger enzymatic system – which includes peroxidase, glutathion peroxidase, catalase, superoxiddismutase – to the electromagnetic exposures of HeLa cells. Thus, we previously signaled, that the:

- cEMF action, upon the HeLa cells cultures, has led to a significant enhancement of the Px activity and to a concurrent inhibition of the GSH-Px and CAT activities;
- dcEMF impact on HeLa cells has conditioned a significant intensification of the Px and CAT activities, or a simultaneous repression of the GSH-Px activity. We must specify that the SOD activity was not significantly modulated by the EMF irradiation, applied in our experimental conditions.

The intracellular presence of some minimum amounts of hydrogen peroxide, superoxide anions, hydroxyl radicals, lipidic peroxides – natural bioproducts resulted from oxygen normal metabolism – indicates the metabolic state of a cell. For the prevention of the cytoplasmic acidification, the eukaryotic animal cell holds specific clearing enzymes, which maintain the intracellular medium homeostasis catalyzing the reduction reactions of these reactive oxygen species (ROS). The submission of healthy cells to the oxidative stress generates high quantities of ROS, mobilizing the free radicals scavenger enzymatic army by negative feedback mechanism stimulating the biosynthesis and activity of implied enzymes.

Our above mentioned experiments have highlighted that the c and dcEMFs modulates the activities of some oxidative stress enzymes (Px, GSH-Px and CAT), either in a stimulatory or inhibitory sense, the effect amplitude being statistically and cytostatically significant. Therefore, it seems probable that the electromagnetic irradiation of low intensity and frequency – used as cytostatic treatment – has altered the unfolding of the metabolic events generating high intracellular amounts of free radicals, which have activated or repressed some oxidative stress enzymes. This effect of EMFs – which can partially explains their cytostatic action – can be the result of an indirect or direct interaction of the electromagnetic energy with the enzymatic biomolecules.

In favor of our assumption, regarding the implication of a oxidative stress mechanism in the expression of EMFs cytostatic property, come the experimental data upon the lipid peroxidation reactions in the presence of the intracellular O_2 reactive species, which form the MDA molecules. Indeed, the cEMF treatment has been correlated with an increase in MDA production.

The bulk of the present experimental results highlights and quantifies the modulation of some enzyme activities by the low frequency and intensity electromagnetic fields with 60 minutes continuous or discontinuous action upon the HeLa cells cultures, also confirming and reconfirming the interaction between this physical agent and tumoral cells, as well as the cytostatic impact of the EMFs.

The interference of the electromagnetic fields with different enzymatic activities of the HeLa neoplastic cell would be mediated by cell membrane, its interaction primary site value being due to the plasmalemma electrical properties , the intramembranary localization of receptor ends of intra- or extracellular signaling networks and to the membrane capacity to generate cascade responses with echo in entire cell. Our assumption is sustained by the modifications in

activity of some membrane associated enzymes (Na^+-K^+-ATP-ase and ALP), these being obvious and having direct consequences upon metabolic processes, which generate the ROS mechanism.

Another plausible hypothesis regarding the possible mechanism of action of EMFs, involved both in modulation of enzymes activities and in expression of their cytostatic property, is related to a possible direct interaction of EMFs with the intracellular receptors. In other words, after their intracellular deep penetration, the electromagnetic waves interact with DNA, RNA, proteins or enzymes, influencing their functional state and activating some genetic or metabolic mechanisms responsible of EMF cytostatic property.

CONCLUSIONS

The short lasting *in vitro* electromagnetic treatment of the HeLa human tumoral cells modulates the activity of some enzymatic systems, located either at membrane level or at intracellular one.

Stimulation or inhibition of LDH, ACP, ALP, Px, GSH-Px, CAT, SOD enzymes and of lipid peroxidation reactions have modified the membrane and metabolic processes, justifying the cytostatic impact of the low intensity and frequency electromagnetic energy with continuous or discontinuous action, its potential being dependent on the EMF type .

The cytostatic property of the EMFs is probably due to a membranotrop action mechanism and/or metabolic action mechanism of the electromagnetic waves, which can interact with the membrane receptors and/or intracellular ones.

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