MODULATION OF SOME MEMBRANARY AND METABOLIC PROCESSES OF HeLa TUMORAL CELLS BY ELECTROMAGNETIC FIELDS OF LOW FREQUENCY AND INTENSITY

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Abstract: The present paper represents the result of a study on the HeLa neoplastic cells' membranary and metabolic reactivity to the action of non-ionizing electromagnetic field of continuous or discontinuous type. The *in vitro* short-lasting electromagnetic field exposure of the human tumoral cells has induced a significant modulation of the membrane Na^+-K^+-ATP-ase activity, comparatively with the control level. The same electromagnetic treatment has also conditioned an alteration of the control metabolic profile. Thus, we have appreciated a stimulation of the glycogenesis, lipogenesis, proteinsynthesis and nucleic acids biosynthesis, correlated with an intensification of the intracellular consumption – on catabolic and/or anabolic pathways – of the glucose, lactic acid, free fatty acids and aminoacids. The direction and amplitude of the modifications of the HeLa cellular processes are dependent to the type of electromagnetic field application.

INTRODUCTION

In the past few decades, the substantial presence of non-ionizing electromagnetic fields (EMFs) or radiations in the environment and the possible harmful impact of the electromagnetic pollution upon health have promoted studies on bioactive effects of this ambient medium factor upon the biological systems to ensure an efficient protection of the human health state [Ailiesei, 1996; Chionna et al., 2005; Dini L. and Abbro, 2005; Guimaraes and Linden, 2004; Jaite et al., 2002; Jitariu, 1987; Karasek and Lerchl, 2002; Rosen, 2003; Tenuzzo, 2006; Wartenberg, 2001; Zamfirescu et al., 2000].

Thus, the investigations *in vitro*, on different cell line types (normal, stabilized or transformed), and *in vivo*, on various living animal organisms have revealed that the EMFs induce some positive/negative, reversible/irreversible structural/functional modifications with intra- or extracellular expression, unquestionably proving the interaction between EMFs and cellular, subcellular and molecular structures of the animal cells [Abbro et al., 2004; Ailiesei, 1996; Chionna et al., 2003, 2005; Dini and Abbro, 2005; Jitariu, 1987; Marinelli, 2004; Pagliara et al., 2005; Tarantino et al., 2005; Tenuzzo et al., 2006; Zamfirescu, 2000].

At the current stage of knowledge in this fascinating and considerably interesting research topic still remain many gaps regarding the induction mechanisms of physiological effects by electromagnetic fields. Consequently, the extending and thoroughgoing of the investigations are necessary for: elevation of the status of bioelectromagnetic research; explanation of the direct transmission of the electromagnetic energy to the reactive biological systems; the establishment of proper experimental approaches to evaluate the real bioactive potential of the electromagnetic exposure.

In this informational frame we must draw attention to the fact that there aren't any systematic and complete studies in the specialty literature, which characterize the electromagnetic field as a cytostatic agent, although the reactivity of some cellular processes of the tumoral cells to the electromagnetic impact is mentioned. Therefore, our research team began a complex study of the interaction of the EMFs with cellular, subcellular and molecular structures as well as with cellular processes of the tumoral cells, in order to establish the therapeutic significance of the EMF as singular cytostatic agent or as physical association agent with oncotherapeutic drugs for improving the struggle against neoplastic scourge.

The aim of the present work was to investigate the effect of some non-ionizing electromagnetic fields, with low frequency and intensity, upon some membranary and metabolic processes of the HeLa cancerous cells.

MATERIALS AND METHODS

The biological material used in the *in vitro* investigations was represented by HeLa cellular cultures of human neoplastic origin (uterine cervix carcinosarcoma). The test flasks of 150 cm^2 have been inoculated with 2 x 10^6 tumoral cells in Eagles' MEM growing medium supplemented with 10% calf serum, penicillin and streptomycin solution 100 I.U./ml and nystatin antimycotic solution 10.000 U/ml. The cells were incubated at 37^0 C for a culture development period of 72 hours**.** When the monolayer stage was attained, the cultures were divided into control and "treated" cultures.

The electromagnetic field (EMF) of continuous or discontinuous type (cEMF; dcEMF) was 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 biological material during to the electromagnetic treatment. The intensity and frequency of the generated EMF were of 5.5 mT and 100 Hz.

Single EMF was applied continuously or discontinuously (with breaks of 1 second and action 3 seconds) for a period up to 60 minutes to the "treated" 72 hours cell cultures. 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 30^0C.

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 and then subjected to the steps of obtaining the cell clarified lyzates. Adequate aliquots were used for the biochemical determination of the membranary Na^+-K^+-ATP-ase activity and of some metabolic indices [Artenie and Tănase, 1981]: glycogen (G), glucose (g) and lactic acid (L.A.); total lipids (T.L.), free fatty acids (F.F.A) and total cholesterol; soluble (S.P.), unsoluble (U.P) and total proteins (T.P.); deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and total nucleic acids (TNA).

Five flasks of cultures have been used for each experimental group, the results being analyzed statistically by means of Student' „t" test [Snedecor, 1968].

RESULTS AND DISCUSSIONS

In a first test we have investigated the effect of continuous or discontinuous EMF upon the membranary Na^+–K^+–ATP–ase activity – expressed by quantitative and percentage values – of the HeLa tumoral cells, the experimental results being included in Table 1 and Figure 1.

Table 1. The behaviour of the membrane Na^+-K^+-ATP-ase (mg Pi/g protein) of the HeLa neoplastic cells submitted to a single short time treatment with electromagnetic field, applied continuously or discontinuously. Figures in brackets indicate the number of the used cultures for each experimental type.

Culture types	X ± ES	p
Control	80.1 ± 3.91 (5)	–
cEMF	123.9 ± 3.57 (5)	<0.001
dcEMF	68.6 ± 2.20 (5)	<0.01

It can be seen, in Table 1, that the *in vitro* continuous or discontinuous electromagnetic treatment of the 72 hours old HeLa cellular cultures has induced – in the treated neoplastic cells membranes, comparatively with the control level – statistically significant modifications of the inorganic phosphate contents, released by enzymatic hydrolysis of the ATP, their direction and amplitude being dependent of EMF type.

Thus, we assist to an increase (in the continuous electromagnetic application) and a decrease (in the discontinuous electromagnetic application) of the inorganic phosphate, in the cellular membrane substratum. These quantitative variations have revealed either a high activity of the membrane Na^+-K^+ electrogenic pump, in the case of continuous electromagnetic field action, or a low activity of the membrane Na^+-K^+ -ATP-ase in the case of discontinuous EMF action.

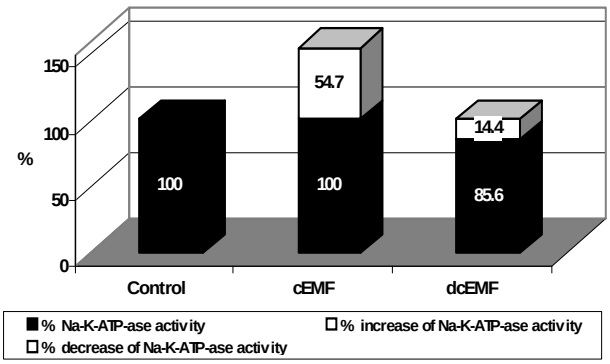

Fig. 1. The modulation of the membrane Na^+–K^+–depending electrogenic pump's activity (%) from the HeLa tumoral cells submitted to the electromagnetic treatment, in comparison with the control cultures.

It can be also highlighted, from the above figure and in comparison with 100% control value, that the membranary Na^+–K^+–ATP-ase activity reaches intensities of 154.7% (cEMF) and 85.6% (dcEMF), respectively, in the case of the HeLa treated neoplastic cells. Therefore, we have appreciated that the electromagnetic field can induce a modulating action upon membrane Na^+–K^+–ATP-ase activity. Thus, the continuous EMF has a stimulatory impact upon the activity of this membrane enzyme and the discontinuous electromagnetic field has an inhibitory impact upon this biomolecule.

In a second step of the research, we have followed the reactivity of the intermediary metabolism of the HeLa tumoral cells submitted to the short-lasting treatment with the 100 Hz and 5.5 mT electromagnetic field, administered continuously or discontinuously. The direction and the intensity of the metabolic processes have been expressed by the quantitative values of some glucidic, lipidic and proteic biochemical parameters (glycogen, glucose and lactic acid; total lipids, free fatty acids and total cholesterol; total, soluble and unsoluble proteins).

Table 2. The effect of unique electromagnetic treatment upon the contents of some glucidic indices (glycogen, glucose and lactic acid, mg/g cellular mass) from HeLa tumoral cell cultures of 72 hours. Figures in brackets indicate the number of experimental cultures for each experimental type.

Culture types	Glycogen		Glucose		Lactic acid	
	X ± ES	p	X ± ES	p	X ± ES	p
Control	13.9 ± 1.6 (5)	-	7.2 ± 2.8 (5)	-	140.4 ± 4.0 (5)	–
cEMF	43.1 ± 3.8 (5)	<0.001	2.6 ± 2.1 (5)	<0,001	95.0 ± 2.8 (5)	<0.001
dcEMF	28.1 ± 2.1 (5)	<0.002	6.8 ± 1.9 (5)	<0,001	103.7 ± 3.2 (5)	<0.001

The *in vitro* electromagnetic treatment of the 72 hours old HeLa cell cultures has induced statistically significant quantitative variations of the glucidic biomolecules. Thus, we registered increases of the glycogenic stock and decreases of the glucose and lactic acid contents, as compared to the control level.

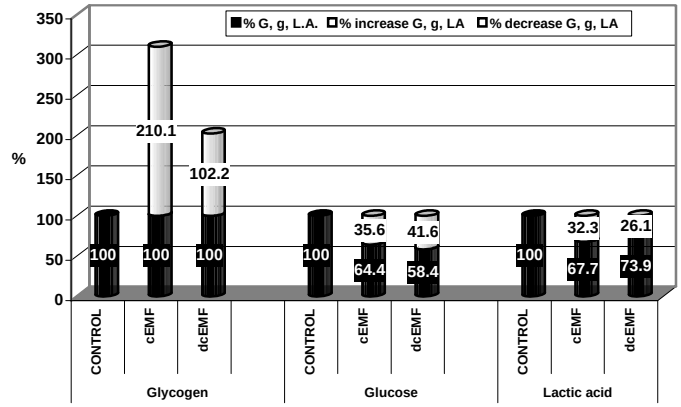

Fig. 2. Percentage variations of the glycogen, glucose and lactic acids concentrations induced by the *in vitro* short-lasting electromagnetic treatment of the HeLa neoplastic cells.

Also, in comparison with the 100% control value, we estimated: an increase of the glycogenic content (of 210.1% and 102.2%), a decrease of glucose (of 35.6% and 41.6%) and lactic acid (of 32.3% and 26.1%) concentrations, the higher variations being registered in the case of the continuous electromagnetic field action. These quantitative and percentage variations of the

glucidic biochemical indices have highlighted the modulation of the cellular glucidic metabolism events, its direction and amplitude being correlated to the EMF type. Thus, it can be highlighted an intensification of the glycogenogenesis, as well as of the intracellular consumption of the glucose and lactic acid, probably in an anabolic and/or catabolic pathway.

Another intermediary metabolism which was investigated is the lipidic one, the pattern of unfolding the biochemical processes in the tumoral cells treated with EMF being illustrated by the parameters: total lipids, free fatty acids and total cholesterol (Table 3 and Fig. 3).

Table 3. Total lipids, free fatty acids and total cholesterol concentrations (mg/g cellular mass) of the HeLa tumoral cells in conditions of the electromagnetic field action. Figures in brackets indicate the number of experimental cultures for each experimental type.

Culture types	Total lipids		Free fatty acids		T Chl.	
	X ± ES	p	X ± ES	p	X ± ES	p
Control	176.7 ± 3.5 (5)	–	72.4 ± 1.9 (5)	–	20.3 ± 1.3 (5)	–
cEMF	239.1 ± 2.7 (6)	<0.001	51.3 ± 1.6 (5)	<0.001	11.8 ± 1.2 (6)	<0.001
dcEMF	198.1 ± 2.4 (5)	<0.001	50.2 ± 1.5 (5)	<0.001	18.3 ± 1.3 (5)	NS

The *in vitro* short time electromagnetic treatment of the HeLa cells has induced the perturbation of the lipidic metabolism. The interference of EMF with the metabolic cellular processes was materialized by intracellular accumulation of the total lipids as well as depletion of the free fatty acids and of the total cholesterol stocks. Thus, as compared to the control values, the intracellular total lipids amount has presented a significant increase (35.3%, in the case of continuous electromagnetic field and 12.1%, in the case of discontinuous one) while the contents of the free fatty acids (29.2% after continuous electromagnetic treatment and 30.7% after discontinuous electromagnetic treatment), total cholesterol (41.9% and 9.9% after both treatment types) have registered a significant decrease. The quantitative and percentage variation of the lipidic biomolecules – of negative or positive direction and with moderate degrees – has emphasized: the intensification of the intracellular lipogenesis; the metabolic utilization of the free fatty acids; the inhibitory effect upon cholesterol biosynthesis.

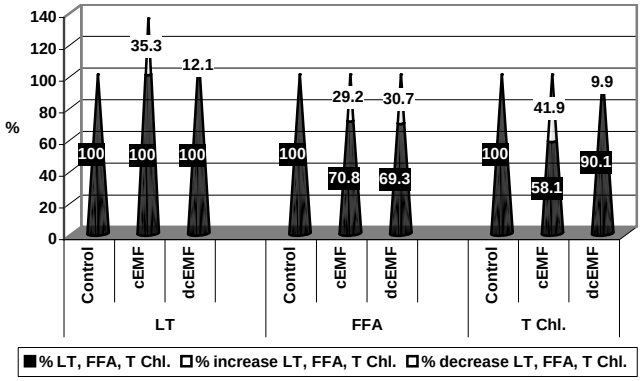

Fig. 3 The direction and the amplitude of the lipidic metabolism modulation, in the malignant HeLa cells, by the electromagnetic field applied continuously or uncontinuously.

The study of the intermediary metabolism of the HeLa tumoral cells, submitted to the unique action of the 100 Hz and 5.5 mT electromagnetic field, was extended by the investigation of the protidic metabolism reactivity. The development of the metabolic events was analyzed on the

basis of the cellular proteic contents variations, these being estimated in comparison to the control values of the soluble, unsoluble and total proteins (Table 4 and Figure 4).

The HeLa cellular cultures treated with electromagnetic field – applied continuously or discontinuously – have been characterized, as compared to control value, by significantly

Table 4. Soluble, unsoluble and total protein contents (mg/g cellular mass), of the 72 hours HeLa tumoral cells cultures, treated with continuous or discontinuous electromagnetic field. Figures in brackets indicate the number of experimental cultures for each type.

Culture types	Soluble proteins		Unsoluble proteins		Total proteins	
	X ± ES	p	X ± ES	p	X ± ES	p
Martor	47.7 ± 2.3 (5)	–	25.1 ± 1.9 (5)	–	72.8 ± 3.1 (5)	–
cEMF	69.4 ± 2.7 (5)	<0.001	32.4 ± 1.6 (5)	<0.001	101.8 ± 4.3 (5)	<0.001
dcEMF	127.6 ± 3.1 (5)	<0.001	37.6 ± 2.1 (5)	<0.001	165.2 ± 5.5 (5)	<0.001

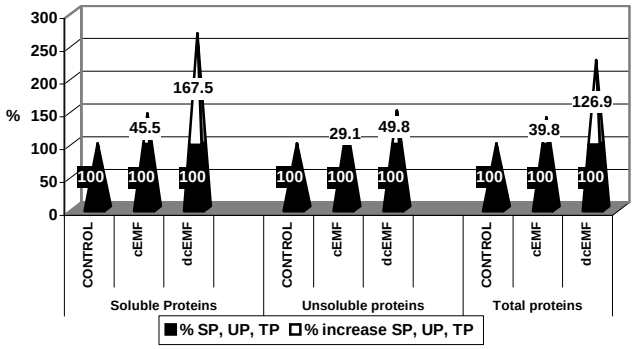

Fig. 4 Procentual variation of the soluble, unsoluble and total proteins in the HeLa neoplastic cells submitted to the *in vitro* short time electromagnetic treatment.

increased contents of the soluble, unsoluble and respectively total proteins. Thus, the percentage variations have reached levels of: 45.5%, 29.1% and respectively 39.8%, in the case of continuous electromagnetic treatment, and 167.5%, 49.8% and respectively 126.9%, in the case of discontinuous electromagnetic field. Consequently, the stimulatory impact of the electromagnetic field upon the cellular proteinsynthesis was suggested.

In order to obtain supplementary information about the interference of EMF with the HeLa tumoral cell metabolism we decided to investigate some aspects of nucleic acids metabolism in this experimental model. The cytophysiologic behaviour of the nucleic macromolecules in the HeLa malignant cells, submitted to the electromagnetic treatment, can be appreciated on the basis of the direction and intensity of the metabolic events.

The experimental results have highlighted, once again, the metabolic impact of EMF. Thus, we registered, in comparison to the control values, higher DNA, RNA and TNA amounts, in the case of the action of the 100 Hz electromagnetic field administered continuously.

Table 5 Concentrations, mg/g cellular mass, of the DNA, RNA and TNA macromolecules from the HeLa tumoral cells submitted to the electromagnetic treatment. Figures in brackets indicate the number of experimental cultures for each type.

Culture types	DNA		RNA		TNA	
	X ± ES	p	X ± ES	p	X ± ES	p
Control	3.1 ± 1.6 (5)	-	3.3 ± 1.8 (5)	-	6.4 ± 2.4 (5)	–
cEMF	3.4 ± 1.5 (5)	NS	3.6 ± 1.9 (5)	NS	7.0 ± 3.1 (5)	NS
dcEMF	3.0 ± 1.3 (5)	NS	3.2 ± 1.6 (5)	NS	6.2 ± 2.7 (5)	NS

Contrary, in the case of discontinuous electromagnetic field, the nucleic acids contents are insignificantly smaller than those of the untreated cultures values. Therefore, an interaction between the electromagnetic field and the nucleic acids metabolism, can be assumed, this materializing itself in a stimulating impact (of about 9.4% for EMF applied continuously) or in

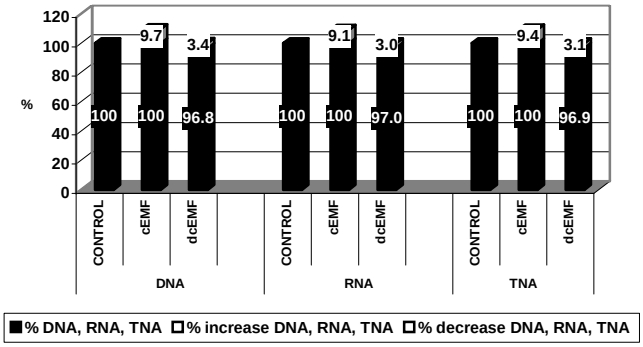

Fig. 5 The direction and the amplitude of the nucleic acids metabolism modulation, in the malignant HeLa cells, by the action of the electromagnetic field.

an inhibitory effect (of about 3.0% for EMF applied discontinuously) upon biosynthesis of the nucleic biomolecules.

At present, 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 the experimental data from biomagnetic research and by their contradictory and heterogeneous character.

The results of the studies – performed on different animal organisms or animal normal cellular systems – have shown both positive (with neurological, endocrinological, immunological, hematological, locomotor expression) and negative (fertility diminution, memory deficiency, growth and development disorders, involvement in the carcinogenetic process) impacts, without the elucidation of the cellular, subcellular or molecular substratum with which the electromagnetic field interact in the starting of these effects [Abbro et al., 2004; Ailiesei, 1996; Chionna, 2003,2005; Dini and Abbro, 2005; Guimaraes and Linden, 2004; Jaite, 2002; Jitariu, 1987; Karasek and Lerchl, 2002; Marinelli et al., 2004; Pagliara et al., 2005; Rosen, 2003, Tarantino et al., 2005; Tenuzzo et al., 2006; Tofani et al., 2003; Wartenberg, 2001].

The reactivity of some cytophysiological processes of the healthy animal cells and its capitalization in different therapeutic purposes (especially in the locomotory disorders) suggested to us the utility and importance of a complex research of 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, in the present work we have investigated the *in vitro* reactivity of some membranary and metabolic processes of the HeLa tumoral cells to the action of two electromagnetic field types (continuous and discontinuous) of low frequency (100 Hz) and intensity (5.5 mT).

Our experimental results, registered after an unique short lasting treatment of HeLa cells with continuous or discontinous electromagnetic field have highlighted a modulation of the membrane Na^+–K^+–ATP–ase activity, comparatively to the one of control. Thus, the continuous electromagnetic field has stimulated the Na^+-K^+ membrane electrogenic pump activity, and the

discontinuous one has an inhibitory impact upon this membranary biomolecule. The intensity of the increasing effect was assessed at 54.7% (EMF continuous), while the depressing effect was evaluated at 14.4% (EMF discontinuous).

The different degrees of membrane Na^+-K^+-ATP-ase activity reveal diverse energeticall needs for the insurance of the 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 primary binding of the electromagnetic energy with the membrane Na^+-K^+-ATP-ase, this enzyme being itself the target of the EMF action.

Our assumption is according to some recent bibliographical information [Dini and Abbro, 2005; Marinelli et al., 2004; Rosen, 2003; Tenuzzo et al., 2006; Teodori et al., 2002; Tofani et al., 2003]. Thus, most of the theories addressing the mechanism of the interaction between biological systems and EMF suggest that the plasma membrane, especially the Ca^{2+} membranary channels, by virtue of their bioelectrical properties, are the site where this physical agent exerts its primary effects. The moderate intensity of the electromagnetic field can affect the rotation, the orientation and disposition of the membrane biomolecules by virtue of their diamagnetic properties. These influences upon the organization of the supramolecular structures would affect the structural and functional state of the membranary Na^+-K^+-ATP-ase. Therefore, plasma membrane structural and biophysical changes would affect, in turn, receptor binding or activation and thereby affect cell function in general. In particular, it has been suggested that EMFs alter the function of the cell’s transmembrane calcium flux in diverse experimental models. Ca^{2+} ions as mediators of intracellular signaling are essence for the development of some cytophysiolgical processes.

Consequently, new values of the extra- and intracellular ionic ratios will be established. These 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 exposure to EMF upon metabolic processes.

Indeed, the comparative analysis of our data, in relation to the control metabolic profile of the untreated HeLa cultures, has highlighted quantitative variations – of different directions and amplitudes – of some glucidic, lipidic and protidic biomolecules and of the nucleic macromolecules. Thus, in the case of the *in vitro* treatment with EMF applied continuously, increased intracellular contents of glycogen, total lipids, soluble and unsoluble proteins, DNA and RNA, as well as decreased stocks of glucose, lactic acid, free fatty acids and total cholesterol were assessed. In addition, in the case of the EMF administered discontinuously augmented intracellular amounts of glycogen, total lipids and proteins as well as small intracellular stocks of glucose, lactic acid, aminoacids, free fatty acids, total cholesterol, nucleic acids were estimated. Therefore, we can appreciate that the electromagnetic field intensifies the glycogenogenesis, lipogenesis and proteoinosynthesis, stimulates or inhibits the nucleic acids biosynthesis, attenuates cholesterolgenesis and activates the intracellular metabolic utilization of the glucose, lactic acid, free fatty acids and aminoacids biomolecules.

Certainly, the intracellular utilization pathways of the above mentioned biomolecules are represented both by the biosynthetic processes of the glucidic, lipidic, protidic and nucleic compounds, and by the energetical processes, the glucose, lactic acid, aminoacids and free fatty acids being sources for the anabolic reactions and, in the same time, fuel resources for the electromagnetic treated cancer cells.

This specific metabolic behaviour of HeLa neoplastic cells, submitted to EMF action, can be the consequence either of a primary interaction of this physical agent with the plasmatic

membrane or a subcellular, intracellular interaction of electromagnetic energy with some molecular structures which modifies the gene pattern expression, the oxygen free radicals production as well as the activity of some metabolic key enzymes [Brune, 2003; Chionna et al., 2003;Gumaraes and Linden, 2004; Marinelli et al., 2004; Stevens, 2004; Tenuzzo et al., 2006].

Indifferently of the cellular level of the primary interaction mechanism, the low frequency and intensity electromagnetic fields have induced obvious, significant and indubitable modifications of the some membranary and metabolic processes, which perturb "the new" steady-state of the tumoral cell, suggesting even an own cytostatic property, dependent by the electromagnetic field type. Therefore, we will evaluate, in another paper, the cytostatic and/or cytotoxic action of the continuous and discontinuous, low frequency and intensity electromagnetic field by investigating its effect upon the development of tumoral cellular cultures, the cell proliferation and viability.

CONCLUSIONS

The short lasting *in vitro* electromagnetic treatment of the HeLa tumoral human cells modulates the membranary Na^+–K^+–ATP-ase activity and, inherently, influences the membrane permeability, their direction and amplitude being correlated to the generating type of EMF.

The continuous or discontinuous electromagnetic field modifies the metabolic profile of the treated HeLa neoplastic cells. The direction and amplitude of the membrane and metabolic effects are dependent of generating type of EMF.

The alterations of the HeLa cells membranary and metabolic processes are due to the interaction of the electromagnetic field with the membrane or intracellular receptors. Thus,a cytostatic and/or cytotoxic property of the EMF can be suggested.

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