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Synergisms of Electric or Electromagnetic Fields and Photodynamic Effects Induce Apoptosis and Necrosis of Cancer Cells

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Abstract: Weak pulsating sinusoidal electromagnetic fields (PEMF) have been applied to change membrane permeation and induction of apoptosis (necrosis). In the case of suspension of human cancer cells U-937 and K-562 inside of Helmholtz-coils the amplitude of PEMF $B = 10$ and at 39mT (at 50 Hz) was combined gradually with the cytotoxic agent actinomycin-C on one hand with its novel photodynamic activity on the other.

Depending on temperature, pH-value and treatment time the necrosis of these cells was determined by means of trypan blue staining as well as the induced apoptosis by FACScan technique. Synergisms were discovered yielding high rates of cell death for three combinations:

I. PEMF + hyperthermia or (and) hyperacidity

II. PEMF + cytostatic drugs in the dark

III. PEMF + cytostatic drugs irradiated by visible light (photodynamic effect)

The selection of cytostatic drugs as actinomycin-C and some anthracyclines was to prove their photodynamic activity, which is suitable to enhance their cytotoxic effects.

These results of inductive coupling (PEMF) were compared with effects of A. C. currents and electroporation by single D. C. pulses between solid electrodes. Contrary to these both methods the PEMF application has a noninvasive influence on the viability of cancer cells suitable therefore to support tumor therapy by this adjuvant bioelectrochemical method.

Key words: PEMF, Electroporation, Actinomycin-C, Photodynamics, Synergism, Cancer cells U-937, K-562

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1 Introduction

Bioelectrochemical methods have been widely used for poration of cell membranes and moreover to kill cells, e.g. by strong pulses[1] or delivery of cancerostatic substances[2]. Another possibility to cause lethal effects in cells and tissues is the classical photodynamic treatment since 1901[3], which requires membrane permeation of an excitable dye (sensitizer) before illumination for subsequent photodynamic destruction of biopolymers inside the cells[4,5].

The combination of electric and electromagnetic treatment with excitation of certain dyes and some cytostatic agents[5] achieves a maximum of strong apoptosis[6] and necrosis of cancer cells.

The results of treatment of human U-937 and K-562 cells by

A) single d.c. electric pulse beween electrodes in cell suspension[7]

B) alternating current between electrodes in cell suspension

C) inductive coupling by Helmholtz-coils or solenoids[8] around the cell suspension will be presented synergistically with the cytostatic actinomycin-C and of some selected anthracyclines

Our aim is to compare the present electrochemotherapy by electroporation of membranes with new possibilities of noninvasive treatment of inductive coupling by producing magnetic flux densities B between 10 and 39 mT.

2 Materials and Methods

2.1 Direct Current Method (A)

The electroporation was performed by the BTX Electro Cell Manipulator-600 (Genetronics, San Diego) equipped with a generator of exponentially decaying pulse and a cuvette with embedded aluminium electrodes of 0.2 cm distance[4]. The experiments were carried out in a low output voltage mode at ambient temperatures of 25 ℃. Cell suspension (200 μL) in the presence of a cytostatic substance (Daunomycin-HCl and Actinomycin-C) were subjected to one pulse (field strenght E = 1.2～1.4 kV/cm and exponential pulse duration (1/e) of 0.5～3 ms).

2.2 Alternating Current Method (B)

The alternating current on cell suspension were carried out in the same cuvettes with embedded aluminum electrodes of 0.2 cm distance, using a frequency generator (Oscillator B492) combined with the Amplifier PA 940 (Conrad-Electronics, Hirschau).

This above equipment produces sine waves, which were tested in the frequency range between 4 Hz and 32 kHz with amplitudes between 15 mA and 65 mA. Finally a synergism of A.C. field and added cytostatics was investigated under the optimal conditions: 16 kHz, 55 mA for 20 min treatment in nutritional medium.

2.3 Alternating Field Method (C)

For inductive coupling of electromagnetic fields[8], two kinds of Helmholtz-coils and solenoids were used in connection with sine wave transformers (Conrad Electronics, Hirschau)[5]:

—for 39 mT, equipped with air and water cooling, thermostated for 37 ±0.2 ℃ (optimal temperature) or 42 ±0.2 ℃ (hyperthermia) of the sample

—for 10 mT combined with the irradiation equipment at room temperature. On the optical bench were clamped: the lamp (24V, 150W, tungsten-halogen HLX) from Osram; continuous emission in the visible range: irradiance at cell suspension 55 mW/cm^2; the water cuvette (7 cm thickness); the focussing lens; the acryl-microcuvette for 100 μL suspension inside the Helmholtz-coil surrounded by a cylindrical water thermostate. The temperature inside the cuvette was practically the same as that of the thermostate

The maximum of magnetic flux density B was controlled by the Teslameter FM210T (Projekt Elektronik, Berlin).

The cell suspension itself and in the presence of actinomycin-C was exposed to PEMF for 30, 60 or 120 min respectively.

In the tables: E is the mean percentage of dead (necrotic) cells stained by trypan blue in the experiment (5～7 repetitions); C is the mean percentage of dead cells in the control. After each measurement always 4 counts of > 100 cells under the microscope were necessary. The percentage of necrotic cells (mostly 1.4 % for K562, 8 % for U-937) in cultural suspension at the beginning and after 24 h were always subtracted from C and E values determined by trypan blue coloring. The field efficaly itself E_f was calculated according to $E_f = (E/C - 1) \cdot 100\ \%$.

2.4 Flow Cytometry (FACScan)

For determination of apoptosis and necrosis, the flow cytometry was performed using the FACScan (Becton Dickinson, San Jose, CA) and the dyes annexin and propidium iodide[6], about 1 hour after the experiment.

2.5 Cells and Media

The human histiolytic lymphoma U-937 Cells with mononuclear phagocyte characteristics were taken from the American Cell Culture Collection. Cultivation occurs in RPMI 1 640 medium supplemented with 10 % fetal calf serum (Gibco Life Science, USA), 100 mg/ml streptomycin and 100 Uml^{-1} penicillin (Sigma, USA) at 37 ℃ in a 5 % CO_2 incubator of 90 % humidity.

The human myeloid leukemia K-562 cells were from Fujisachi Cell Center (Japan). The culture medium was 90 % RPMI (Gibco) with 10 % CO_2 at 37 ℃.

2.6 Drugs and Chemicals

The following drugs and chemicals were used in 0.3 or 0.6 mol/L mannitol/water solutions: daunomycin, aclacinomycin, adriamycin, carminomycin, (Serva, Heidelberg, Germany); actinomycin-C (2 % ethanol or 10 % DMSO solution, Mw 1 300, HKI, Jena, Germany); buffer (pH = 5.2, 0.1 mol/L $NaH_2PO_4 \cdot 2H_2O$, 0.1 mol/L KCl, conductivity: 10.4 ms/cm); Trypan Blue (Mw 960.8, Sigma, Deisenhofen, Germany) in concentration of 0.2 % was used for determination of the necrosis. For "hyperacidity" of pH 6.5 condition the cell suspension in culture medium was mixed with phosphate buffer

(conductivity of 15 ms/ cm).

2.7 Photodynamic Treatment

Finally, the cell suspension in presence of actinomycin-C or an anthracyclin was irradiated by the mentioned white light tungsten lamp, which photooxidizes e. g. guanine of DNA, causing DNA strand breakage and cell death by two mechanisms:

Type I: photooxidation of cell components by sensitizers (S) excited between 400～800 nm[9], simplified:

$$^3S + O_2 \longrightarrow {}^{\cdot}S^+ + {}^{\cdot}O_2^-$$

$${}^{\cdot}S^+ + G \longrightarrow S + {}^{\cdot}G^+ \qquad \text{or first by energy transfer to } O_2$$

Type II:

$$^3S + O_2 \longrightarrow S + {}^1O_2$$

$${}^1O_2 + G \longrightarrow {}^{\cdot}O_2^- + {}^{\cdot}G^+$$

with S, ^{3}S-sensitizer and its triplet state;

G, $^{\cdot}G^+$-guanin, its radical leads to splitting of the DNA backbone; O_2, $^1O_2$, $^{\cdot}O_2$-oxygen, its singlet state and one of possible radicals.

Type I mechanism needs penetration of S through the cell envelope for complex formation with biopolymers inside, whereas type II oxidizes compounds also on the cell surface or inside by faster diffusion of $^1O_2$.

3 Results

The combinations of three bioelectrochemical methods A), B), C) with the photodynamic effects on cancer cells will be presented step by step and the results are shown in terms of trypan blue staining of necrotic cells or FACScan determination for apoptosis and necrosis.

3.1 Single high electropulse for electroporation and sensitizer delivery(A)

The highest lethality of practically 100 % of cancer cells can be reached by the synergism of the pulse and light applied nearly simultaneously on cell suspension containing the sensitizer[4]. However, in order to see the proportionated efficacy of pulse and light stepwise actions were performed.

Fig. 1 shows the results determined by trypan blue staining. Applying the pulse (1. 4 kV/ cm, 1. 6 ms) about 37 % of K-562 cells are blue, however, after 20 min only 16 % are not able to reseal their membranes, that means they are dead. Actinomycin-C yields less dead cells without pulse(control), but more than 50 % dead cells as the result by electroporation.

Finally, 85 % of dead cell by the photodynamic activity of actinomycin-C were counted after irradiation of the same suspension for 20 min. This method will be not only effective for combination with electroporation for cancer therapy[2], but is moreover effective to deliver also macromolecular sensitizers (Mw ≤500 000) into cells[10]. The response of cells is somewhat weaker for daunomycin and the mentioned anthracyclines (not shown here) than for actinomycin-C.

The FACScan determination shows more details as trypan blue staining. For instance, a double pulse (1.4 kV/cm, 3 ms) decreases 95 % of vital cells from the beginning (besides 2.1 % necrotic, 2.4 % apoptotic) to 60.5 % vital, 19.5 % necrotic and 8.7 % apoptotic cells, besides about 11 % ruptured cells.

3.2 A. C. between electrodes in cell suspension(B)

Optimal condition were found for frequency (16 kHz), amplitude (55 mA) and time (20 min). Fig. 2 shows the percentage of lethality for U-937 cells by this field alone and in the presence of actinomycin-C and daunomycin in comparison to both cytostatic agents without any current treatment (control).

In the FACScan diagram (Fig. 3) about 1 hour after this A. C. treatment more details can be seen than with trypan blue staining indicating only the necrotic part of the cell population.

According to Fig. 3 this soft method B) produces more apoptotic and necrotic cells than the short pulse yielding electroporation A), however, without ruptured cells. Therefore the sum of all cells in the quadrants is 99.97 %.

Additional necrosis can be produced by visible light irradiation, too.

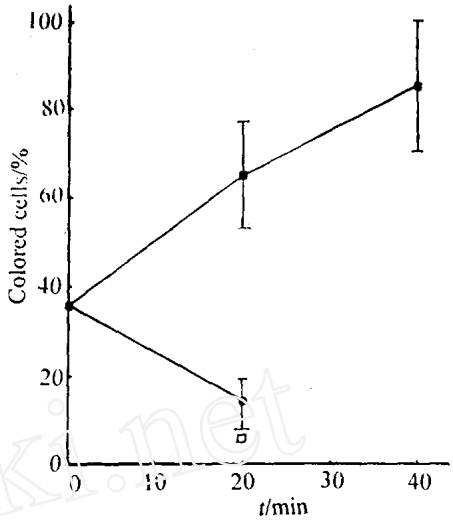

Fig. 1 Step by step electroporation and irradiation of K-562 cells. Cell death by 4×10^{-4} mol/L actinomycin-C (■) 20 min after the pulse (1.4 kV/cm) and followed by the additional photodynamic killing effect of further 20 min duration (40min after pulse). Nutritional medium and phosphate buffer (pH 6.5).
● dead cells by pulse after 20min waiting time for resealing the membrane without actinomycin-C
□ dead cells by actinomycin-C alone without pulse in the dark.
Between ■ (shortly after the pulse) and ● there is the resealing time of 20 min.

3.3 Inductive coupling by Helmholtz-coils around the cell suspension(C)

This noninvasive method in contrast to[2] induces also apoptosis and necrosis not only of suspended cancer cells but also inside animal tumors[12,13] besides inhibition of angiogenesis[13]. The following levels of application have been studied:

—C_1 the synergism of field effect with hyperthermia and hyperacidity.

—C_2 synergism of field effect and actinomycin-C in the dark.

—C_3 synergism of field effect and the photodynamic activity of actinomycin-C.

(1) C_1 level

In agreement with results from[11] the induction of apoptosis by PEMF can be determined by trypan blue staining of dead cells, however, mostly later after the treatment, e.g. 24 h.

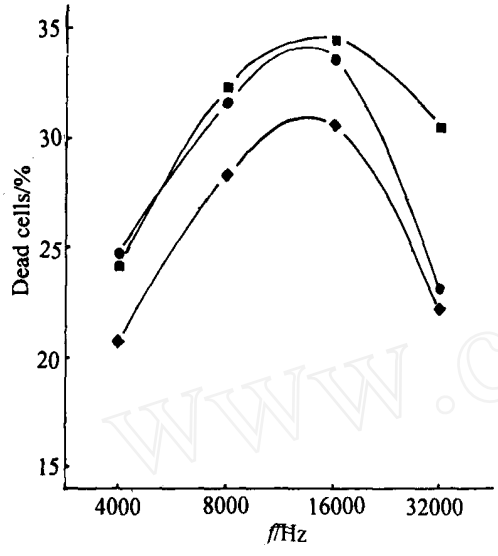

Fig. 2　Influence of frequency on the U-937 cell viability. The lethal effect by penetration of the drugs into the cells for 20min without field below left(□) for actinomycin-C (1×10^{-5} M) and (○) for daunomycin (1×10^{-5} M) as control. Lethal Effect of 20 min a. c. field alone 55 mA, 16 kHz(◆). Synergism of 20min field and drugs (■) for a. c. field plus actinomycin-C (1×10^{-5} M) and (●) for field plus daunomycin (1×10^{-5} M). (The K-562 cells show about the same sensitivity)

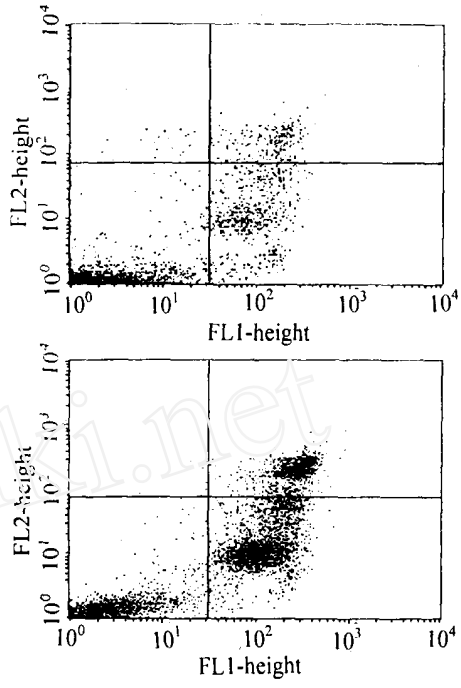

Fig. 3　Percentages of apoptotic and necrotic U-937 cells according to the FACScan determination:
Control (upper curve): suspension before the treatment: UR2. 7 % necrotic cells, LL 89. 86 % vital cells, LR 7. 17 % apoptotic cells
Experiment (lower curve): 20 min treatment by 55 mA at 16 kHz: UR22. 4 % necrotic cells, LL 32. 71 % vital cells, LR 44. 67 % apoptotic cells

The results are presented in Tab. 1 at 37 ℃ and 42 ℃. The efficacy rises, if PEMF is combined with hyperthermia(≥42 ℃) or hyperacidity (pH was decreased from 7. 4 of nutritional medium to 6. 5) or both according to the therapy conception of M. V. Ardenne, under which conditions cancer cells react more sensitive by both changes than normal cells[15], which is the reason for a quite strong difference between their vitality. Whereas the necrotic effect of B = 10 mT at 37 ℃ during 1 h is negligible but not after 3d fermentation. For B = 39 mT a doubling of E/C can be reached during 3 h treatment under conditions of hyperthermia and lowered pH-value (hyperacidity). FACScan diagrams correspond to Fig. 3.

Tab. 1 Synergism of PEMF and hyperthermia and hyperacidity depending on temperature and pH

B/ mT	temperature/ ℃	time/ min	pH	*C*/ %	*E*/ %	*E*/ C(after 24 h)	E_f/ %
39	37	180	7.4	9.3 ±2	14 ±2.2	1.5(27 ℃)	+ 50
	37	180	6.5	12.3 ±2.5	23.5 ±3.5	1.9(27 ℃)	+ 90
	42	180	6.5	19.4 ±3.5	52.3 ±4.5	2.7(27 ℃)	+ 170

Note: percentage of lethal effect of PEMF itself on K-562 cells, measured by trypan blue after 24 h at room temperature (27 ℃). *E* means with field, *C* without field. Nutrition medium: pH 7.4 or with Phosphatbuffer pH 6.5. E_f: the field effect itself. SD values from 4 countings. $P < 0.05$

(2) C_2 level

In this combination of actinomycin-C and PEMF both mechanisms yield apoptosis besides by necrosis. Typical results are shown in Tab. 2. The *E*/ *C* values at both temperatures are similar because the apoptose induction activity by actinomycin-C increases proportionally with concentration.

Tab. 2 Synergism of PEMF and cytotoxic effects, percentage of lethal (mecrotic) U-937 cells by PEMF plus actinomycin-C (1×10^{-4} mol/ L)

B/ mT	temperatur/ ℃	time/ min	pH	*C*/ %	*E*/ %	*E*/ *C*(after 4 h)	E_f/ %
39	37	30	7.4	17 ±3.9	23.5 ±2.7	1.4	+ 40
	42	30	7.4	24 ±2.6	34.7 ±3.0	1.5	+ 50
39	37	60	7.4	31.2 ±3.1	42.3 ±3.0	1.3	+ 30
	42	60	7.4	40 ±4.0	61.0 ±2.2	1.5	+ 50

Note: *E* means with field, *C* without field; E_f: the field effect itself. K-562 shows similar *E*/ *C* values. Highest *E* values are about 60 % dead cells. SD(4 countings) = ±3.6; $P < 0.05$

(3) C_3 level

Due to the similarity of chromophores of methylene blue and anthraquinone derivatives on one side[4,5] and actinomycin-C and the anthracycline derivatives on the other their photodynamic activities were tested additionally in order to enhance their cytotoxic effects.

Actinomycin-C combinations with PEMF take place as arrangements (Tab. 3 and Fig. 4):

a) 2.3 h PEMF without actinomycin-C, (counted dead cells after 2 h and 6h),

b) 2.3 h PEMF plus actinomycin-C including 0.3 h light treatment (counted after 2.3 h and 6 h).

Tab. 3　Synergistic lethal effects of PEMF, actinomycin-C(1×10^{-4} mol/L). and 0.3 h irradiation by visible light (after 2 h field exposition)

B/ mT	temperatur/ ℃	+ field time/ h	+ light time/ min	*E*/ *C* after (h)
10	27 ℃	1	60	1.2 (2h)
39	37 ℃	2.3 *	20	1.5 (3h)
39	37 ℃	2.3 * *	20	2 (immediately)

Note: Percentages of dead U-937 and K-562 cells are practically the same. The highest *E* values reache ≥85 % dead cells after storage for 24 h at 25 ℃ (not shown here). Control data C with actinomycin, but without field are about 8 %～12 % necrotic cells after 2.3 h.

*) 2 h field without actinomycin-C, but 0.3 h light afterwards.

* *) 2.3 h field with actinomycin-C, including 0.3 h light before the end of field treatment

For comparison to Fig. 1 (electroporation), the Fig. 4 presents PEMF and light effects according to the scheme C_3).

In spite of rather long PEMF treatment for sufficient apoptose induction and necrosis the final lethal effect can reach the same order of magnitude as for electroporation according to method (A). The morphological changes of cell membrane and inner organelles can be seen on Fig. 5 for five cells after treatment, wheras the three in the corners of fig. 5 are still living.

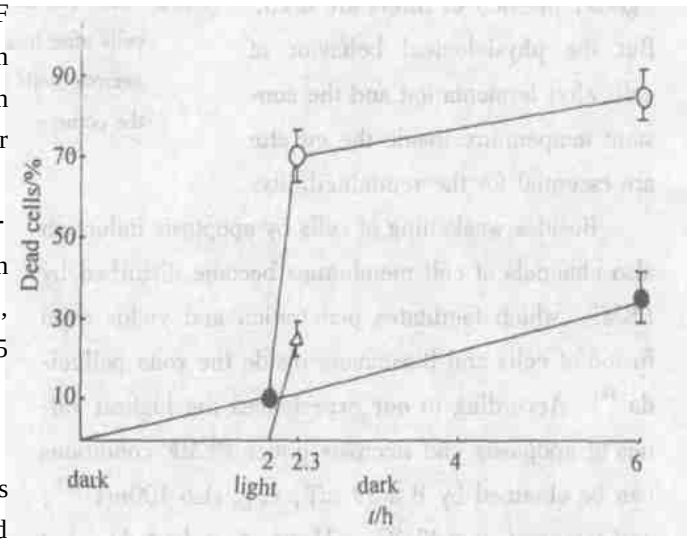

Fig. 4 Step by step exposition of K-562 cells by:

—2 hours treatment with 39mT in presence of 1×10^{-4} mol/L actinomy cin-C and also after 4 hours waiting without field the second determination (●)

—0.3 hours with light (○, after 2 h PEMF) and 4 h later occurs the second determination by trypan blue.

—0.3 hours only light after field: the white triangle(Δ)

For comparison with the electroporation efficacy see Fig. 1

4　Discussion

With the exceptions of continuous D. C. treatment (voltammetry)[16] and capacity coupling, combinations of these three basic bioelectrochemical methods for cancer cell killing were presented on three levels A), B), C). The results of PEMF level C_1 agrees with the paper[11], however, under our conditions the necrosis effects were found also before 24 h waiting. The results of PEMF plus cyto-

toxic agents (level C_2) confirm the tendency of paper[17] using adriamycin against adenocarcinoma. But the results of PEMF plus photodynamic effects (level C_3) show novel possibilities for the synergistic enhancement of killing cancer cells.

Due to so many parameters the optimal conditions must be evaluated in each laboratory. Nevertheless the principal relations between Control and Experiment (E/C and E_f) will be qualitatively the same. It doesn't matter which other PEMF or light sources (LASER), cuvettes (glass, plastic) or filters are used. But the physiological behavior of cells after fermentation and the constant temperature inside the cuvette are essential for the reproducibility.

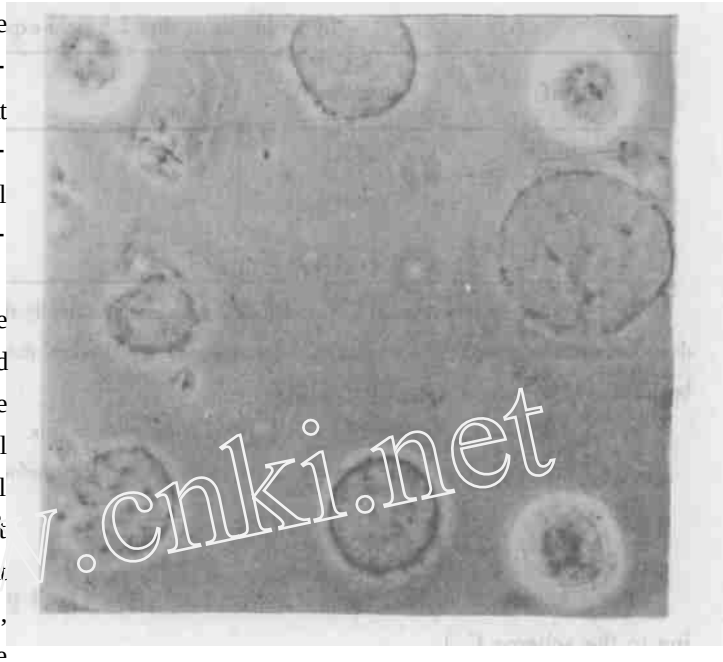

Fig. 5 Phase-contrast photo (total magnification 1 000 x) of U-937 cells after treatment by 10mT for 6h (39 °C). 5 Apoptotic and necrotic cells in the middle, 3 still living cells can be seen in the corners

Besides weakening of cells by apoptosis induction also channels of cell membranes become disturbed by PEMF, which facilitates penetration and yields even fusion of cells and blastomers inside the zona pellucida[18]. According to our experiences the highest values of apoptosis and necrosis under PEMF conditions can be obtained by B ≥39 mT, e.g. also 100mT[19], and temperature ≥42 °C, pH ≤6.5 and t ≥1h, but not below 2 mT[20] and that means hyperthermia and hyperacidity increase stress response (formation of heat-shock proteins) and destabilize membranes additionally as well as the visible-light irradiation (photodynamics) in presence of a dye reacting according to type I or II. Besides the application of 50/60 Hz a frequency dependence has been found on proliferation determined by dehydrogenase production[21]. For future research the frequency depen-

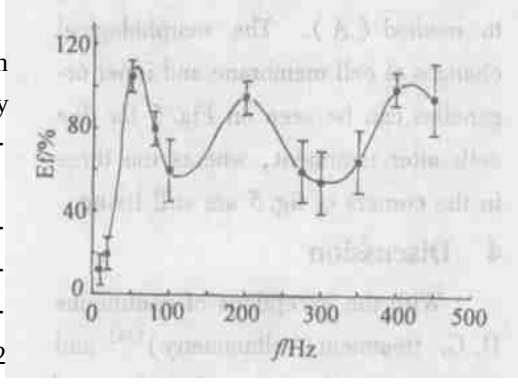

Fig. 6 Frequency dependence of the field efficacy on K-562 cells in 0.3 mol/L manmtol solution. E_f: 9 mT during 20 min irradiation of methylene blue, (5×10^{-4} mol/L) at room temperature. Control 20 min irradiation without field. Field effect itself E_f = 100 % (E/C - 1)

dence should be taken into account because the synergism according to C_3 is not effective below 50Hz as can be seen on Fig. 6 using methylene blue as sensitizer (preliminary results).

Recently we confirmed that normal lymphocytes are much more stable against PEMF treatments than the cancer cells-an essential advantage of this method[21]!

Because PEMF acts noninvasively contrary to[2] and without contamination by electrode products it will be an ideal additional method for tumor therapy in the future[12,14].

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电场或电磁场和光动力的协同效应对癌细胞失活和坏死的作用

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摘要: 应用弱正弦波电磁场改变细胞膜的穿透性并引起其失活和坏死. 研究中 ,将人类癌细胞 U-937 和 K-562 放置于强度为 10 mT 和 39 mT(50 Hz) 的正弦波电磁场内 ,并依次结合细胞毒素放线菌素-C 以及其独特的光动力活性分别进行试验.

关键词: 正弦波电磁场 ;电生孔 ;放线菌素-C ;光动力学 ;协同效应 ;癌细胞 U-937 ; K-562