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Influence of 1 and 25 Hz, 1.5 mT Magnetic Fields on Antitumor Drug Potency in a Human Adenocarcinoma Cell Line

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The resistance of tumor cells to antineoplastic agents is a major obstacle during cancer chemotherapy. Many authors have observed that some exposure protocols to pulsed electromagnetic fields (PEMF) can alter the efficacy of anticancer drugs; nevertheless, the observations are not clear. We have evaluated whether a group of PEMF pulses (1.5 mT peak, repeated at 1 and 25 Hz) produces alterations of drug potency on a multidrug resistant human colon adenocarcinoma (HCA) cell line, HCA-2/1^{cch}. The experiments were performed including (a) exposures to drug and PEMF exposure for 1 h at the same time, (b) drug exposure for 1 h, and then exposure to PEMF for the next 2 days (2 h/day). Drugs used were vincristine (VCR), mitomycin C (MMC), and cisplatin. Cell viability was measured by the neutral red stain cytotoxicity test. The results obtained were: (a) The 1 Hz PEMF increased VCR cytotoxicity ($P < 0.01$), exhibiting 6.1% of survival at 47.5 μg/ml, the highest dose for which sham exposed groups showed a 19.8% of survival. For MMC at 47.5 μg/ml, the % of survival changed significantly from 19.2% in sham exposed groups to 5.3% using 25 Hz ($P < 0.001$). Cisplatin showed a significant reduction in the % of survival (44.2–39.1%, $P < 0.05$) at 25 Hz and 47.5 μg/ml, and (b) Minor significant alterations were observed after nonsimultaneous exposure of cells to PEMF and drug. The data indicate that PEMF can induce modulation of cytostatic agents in HCA-2/1^{cch}, with an increased effect when PEMF was applied at the same time as the drug. The type of drug, dose, frequency, and duration of PEMF exposure could influence this modulation. Bioelectromagnetics 23:578–585, 2002.

Key words: pulsed electromagnetic fields; PEMF; drug resistance; antitumor agents; human colon adenocarcinoma

INTRODUCTION

The resistance of tumor cells to different antineoplastic agents is a major obstacle during cancer chemotherapy. In fact, many patients do not respond to treatments and die due to metastasis, the main mechanism being drug resistance, the so-called multidrug resistance (MDR) phenomenon. The reason for this resistance is the expression of a membrane glycoprotein, named P-glycoprotein or P-170, that acts as a drug extracting pump, reducing the intracellular level of the antitumor agent [Kang and Perry, 1994; Souviron Rodríguez et al., 1997].

Many authors have observed that pulsed electromagnetic field (PEMF) exposure can alter the efficacy of anticancer drugs [Omote et al., 1990; Hannan et al., 1994; Liang et al., 1997; Miyagi et al., 2000], although the interaction mechanisms are still unclear. On the other hand, cells exposed to short and intense electric fields become permeable to different molecules. This phenomenon, named electroporation, is widely used in gene transfection [Miklavcic et al., 1998]. In this way, exogenous molecules like cytostatics can penetrate

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more efficiently by exposure of the cells to a magnetic or electric field, which increases the cell membrane permeability. The higher uptake of drugs enhances cell killing [Hofmann et al., 1999].

On the other hand, it has been reported by other authors that pulsed magnetic fields (5.25 mT peak, 250 pulses/sec) enhance the potency of daunorubicin against KB-Ch^{R}-8-5-11 cells [Liang et al., 1997]. These authors suggest that the mechanism involved may be the inhibition of the efflux pump, P-glycoprotein. In addition, Harland and Liburdy [1997] have observed that 1.2 μT, 60 Hz magnetic fields partially block tamoxifen's inhibitory action on growth of human mammary tumor (MCF-7) cells in vitro. Animal studies have shown that the use of magnetic fields can enhance drug delivery across biological barriers (rat abdominal skin), using benzoic acid as the drug candidate [Murthy, 1999].

HCA-2/1^{cch} is a multiresistant human colon adenocarcinoma (HCA) subline selected by continuous exposure to colchicine. It is also resistant to vinblastine, vincristine (VCR), and mitomycin C (MMC). This cell line expresses P-glycoprotein, and the resistance to cytostatics can be partially reversed by verapamil [Ruiz Gómez et al., 2000].

So far, there have been very few studies that investigate the potential effects of PEMF below 50/60 Hz on drug potency. The purpose of this work is to evaluate whether the low frequency magnetic field (1.5 mT; 1 and 25 Hz) produce, on a multidrug resistant cell line (HCA-2/1^{cch}), alterations of drug potency.

MATERIALS AND METHODS

Cell Culture

HCA-2/1^{cch} cells, a HCA cell line [Ruiz Gómez et al., 2000], were cultured in Dulbecco's modified Eagle's medium nutrient mixture F12-HAM (DME/F12-HAM with L-glutamine and HEPES), supplemented with sodium bicarbonate 7.5% (28 ml/l), 10% heat inactivated calf serum and 1% antibiotic–antimycotic solution (100×) (PSF, GIBCO) at 37 °C in a 5% CO_2/air atmosphere. These cells grow in monolayer and were subcultured with trypsin (0.05%) and EDTA (0.02%) in Dulbecco's phosphate-buffered saline (PBS) [Morales et al., 1995]. This novel colchicine-resistant subline (HCA-2/1^{cch}) in our lab can be obtained by interested investigators.

Magnetic Field Exposure System

The equipment used (Pulsatrón, CEM-84/J; J&J Electromédica; Málaga, Spain) generates rectangular voltage pulses (1 and 25 Hz) that feed two air core coils of 15 cm × 10.5 cm (Helmholtz type), used for the exposure. The generated peak magnetic field between coils was 1.5 mT. Figure 1 shows the voltage waveform applied to the coils; there were groups of 15 rectangular pulses, repeated at 25 Hz, and groups of 20 repeated at 1 Hz.

According to Faraday's Law of Induction, a time varying magnetic field will induce an electric field that is nonuniform in spatial distribution, according to the equation:

$$\xi = \oint \vec{E} \cdot \vec{dl} = -\frac{d}{dt} \iint \vec{B} \cdot \vec{dS}$$

where ξ = induced electromotive force (V), E = electric field (V/m), and B = magnetic field (T).

Considering a circular contour (c) of radius r, coaxial with the coils and parallel to them, the above equation, assuming that the magnetic field is homogeneous in the surface (S) inside the contour, becomes:

$$\xi = E \cdot 2\pi r = -\pi r^2 \frac{d}{dt} B.$$

At these low frequencies, the magnetic field is proportional to the current intensity that flows through the coils (Biot-Savart law) and, therefore, *dB/dt* is proportional to *di/dt*.

Using the above, the ξ waveform in air was visualized and measured in an oscilloscope, for three different radii, by means of a circular pickup coil in air between the coils; qualitatively, it corresponds with the waveform obtained for *di/dt* in a R–L circuit, such as it was in our case. The ξ waveform consisted of pulses

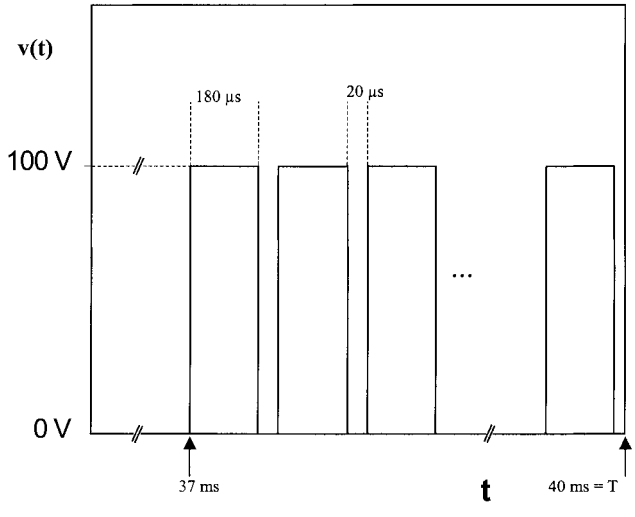

Fig. 1. Voltage source waveform generated by the "Pulsatrón" equipment used. The number of rectangular pulses per group was 15 at 25 Hz and 20 at 1 Hz group repetition, rates.

decreasing exponentially towards zero volts, positive in those intervals in Figure 1 corresponding to the 180 μs when voltage was applied and negative in the 20 μs gaps.

Once the peak values of the positive and negative pulses of ξ were measured, the corresponding peak values of the electric field were calculated from the expression $E = \xi/2\pi r$.

The measurements were made with pickup coils of radii 2, 3, and 4 cm; the results for E were, respectively, 0.5, 0.7, and 0.8 V/m for the positive pulses and 2.98, 3.82, and 3.98 V/m for the negative ones. There were no differences between the values obtained at 25 or 1 Hz.

Nevertheless, these values do not correspond to the electric field experienced by the cells. The cells were cultured in 24 well dishes inside a conductive culture medium, and this modifies the indicated electric field peak values, but not the E field waveform. The effective electric field (E_e) value in each well was measured by means of pickup coils located inside each well. The results obtained for E_e fluctuated from 65 to 260 mV/m during the positive pulse (corresponding to the 180 μs portion of (Fig. 1) and from 650 to 1600 mV/m in the negative pulse zone (corresponding to the 20 μs between rectangular pulses), depending on the spatial location of each well. There were no differences between the values obtained at 25 or 1 Hz.

Cells Exposure Protocol and Current Density

The cells were cultured in 24 well dishes and incubated, during the PEMF exposure, at 37 °C inside a commercial cell culture incubator made of plastic (Thermocult, Boehringer Mannheim, Germany). The magnetic field distribution ran perpendicular to the cell culture surface (Fig. 2). The control cells were placed with no current running through the coils, immediately after the PEMF exposed cells. They were exposed in the same incubator, but not at the same time. Therefore, there was no added artificial magnetic field at the control location. The same passage cells were used simultaneously for their matched sham and exposed experimental groups [Ruiz Gómez et al., 1999]. There was no additional heating due to the activation of the coils, as measured directly by a conventional thermometer.

After monolayer trypsinization, 5000 exponentially growing cells were seeded in each well and were incubated for 24 h at 37 °C, 5% CO_2, to allow the cells to attach. Then, the experiments were performed including exposures to:

A) Drug and PEMF exposure at the same time for 1 h. Then, the cells were incubated for 72 h at 37 °C, 5% CO_2.

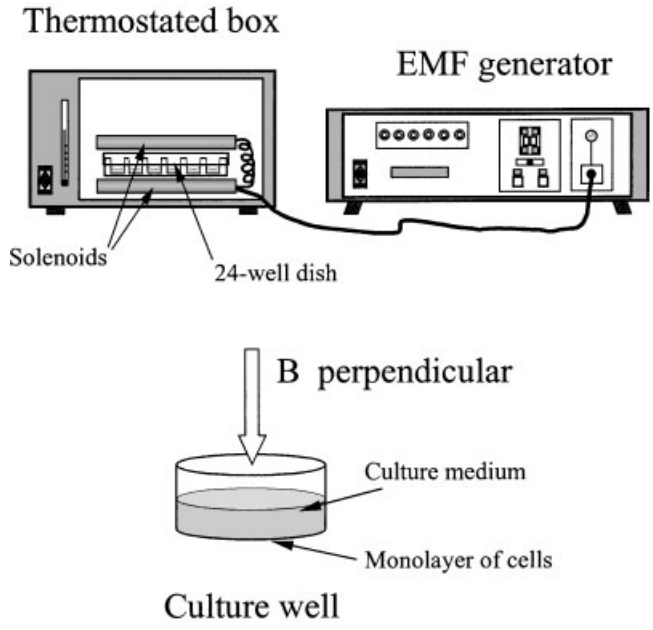

Fig. 2. Magnetic field exposure system.

B) Drug exposure for 1 h, and then exposure to PEMF for 2 h/day for the next 2 days. After this exposure protocol, the cells were incubated for 24 h at 37 °C, 5% CO_2.

Once the incubation period finished, viability was measured by the neutral red stain cytotoxicity test [Babich et al., 1991; Morgan et al., 1991]. Cytostatics used were VCR, MMC, and cisplatin, and the doses assayed ranged from 0.005 to 47.5 μg/ml.

The induced electric current density (mA/m^2) was calculated from the equation $j = \sigma E_e$, E_e being the effective electric field experienced in each well. The conductivity (σ) of a typical culture medium is ~1.5 S/m [Bassen et al., 1992]. The computed peak J values fluctuated from 97.5 to 390 mA/m^2 in the positive pulse period (corresponding to the 180 μs interval of the rectangular pulses) and from 975 to 2340 mA/m^2 in the negative pulse period (corresponding to the 20 μs interval between rectangular pulses). There were no differences between the values obtained at 25 or 1 Hz.

The cells in this study were on the bottom of the dish in a rather concentrated manner, and growing in a close packed geometry. The current density calculated, thus, really does not accurately reflect the current density experienced by the cells located on the bottom of the dish surface because of this geometry. This is an important problem of cell culture dosimetry, since we assume that the cells do not represent a significant volume element and, thus, do not contribute significantly to the conductivity of the medium. Therefore, the

calculated current density relates really only to the cell culture medium, not to the cells themselves in a monolayer on the bottom of the dish. The applied magnetic field penetrates the cells and cell culture media uniformly.

In Vitro Cytotoxicity Assay

The cytotoxicity test with neutral red stain [Babich et al., 1991; Morgan et al., 1991] was applied to measure cell viability. This is a test based on the lysosomal adding of supravital neutral red stain, which quantifies the number of viable cells after exposure to a physical or chemical agent. The quantification of the stain extracted from cultured cells has been shown to be linear with the number of viable cells through direct count [Babich et al., 1991]. This endpoint was observed to show a linear response of the dye uptake to actual cell number, for the HCA-2/1^{cch} cells, as shown in Figure 3. The linear correlation coefficient was $R^2 = 0.9956$.

For this assay, the culture medium was replaced by 1 ml of supplemented fresh medium with 40 μg/ml neutral red. The new medium had been previously incubated 24 h at 37 °C and centrifuged at 2500 rpm for 10 min to avoid crystalline stain precipitates. After 3 h of plates incubation in the absence of PEMF, for both, the sample and control sham exposed cells; the culture medium was removed and cells were washed in 1 ml of fixative (1% $CaCl_2$: 0.5% formaldehyde). Then, 1 ml of 1% acetic acid: 50% ethanol solution was added to each well in order to extract the stain [Fautz et al., 1991]. After 10 min at room temperature and subsequent shaking, the optical density (OD) was measured at 540 nm. The mean OD in the control cells without drug determined after incubation was regarded as 100%; and the percentage of survival at each drug dose was calculated.

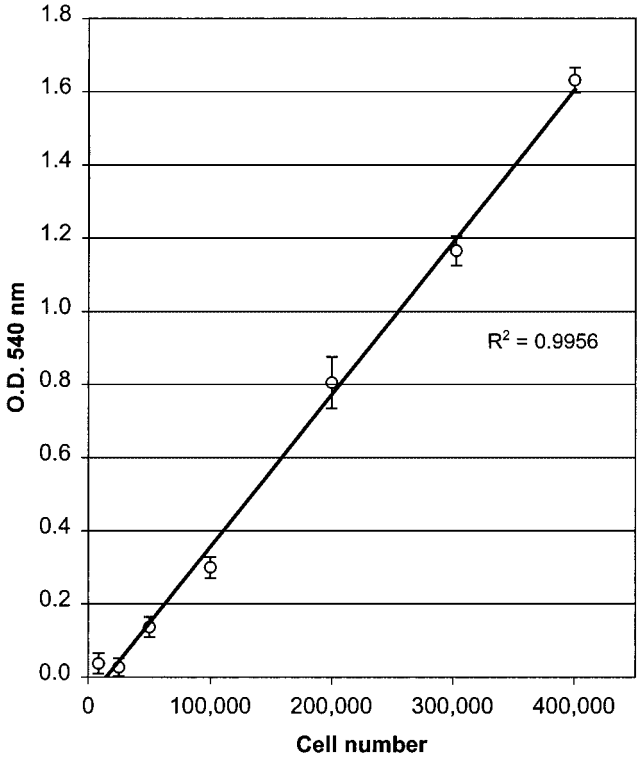

Fig. 3. Linear response of the neutral red uptake to actual cell number of the human colon adenocarcinoma HCA-2/1^{cch} cells.

Growth Curve of HCA-2/1^{cch} Cells

To study the growth pattern of this cell line, 5000 exponentially growing cells were seeded in each well of a 24-multiwell dish. The dishes were incubated and the number of cells counted by means of a hemocytometer (improved Neubauer), until the plateau phase was reached.

Statistical Analyses

The Wilk–Shapiro ranked-plot test was used to assess the normal distribution of the data. Additional statistical analyses were made with the Student's *t*-test. Differences were considered significant when $P < 0.05$.

RESULTS

Growth Curve of HCA-2/1^{cch} Cells

Figure 4 shows a typical growth curve obtained for HCA-2/1^{cch} cells, showing how the cells move through lag to exponential phase and to plateau phase for the seeding density of 5000 cells. The exponential growth phase (log phase) was initiated on the second day of culture, and the plateau phase was reached on the sixth day.

Effect of PEMF on Cell Proliferation

As shown in Figure 5, PEMF exposure did not produce alterations in cell proliferation at 1 or 25 Hz, for both PEMF exposure periods: (1 and 2 h/day: 2 days); as measured by the neutral red cytotoxicity assay. These studies were made in drug free medium, and the evaluation of the number of viable cells after a particular time was considered as indicative of cell proliferation. The incubation time at which the determination was made, after PEMF exposure was started, was 72 h for the group treated with PEMF during 1 and 48 h for the group treated during 2 days (2 h/day).

Effects of PEMF on Antineoplastic Drug Potency

Drug and PEMF exposure at the same time during 1 h. The first exposure protocol assayed was the simultaneous exposition of HCA-2/1^{cch} cells to the

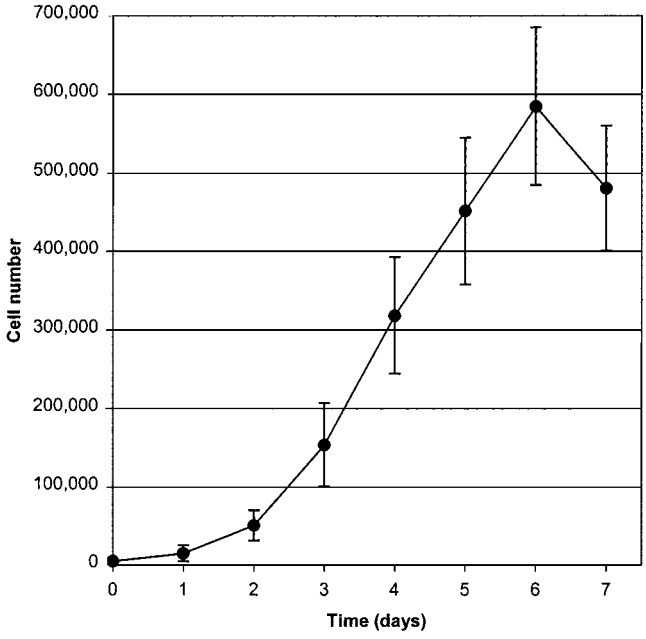

Fig. 4. Growth curve of HCA-2/1^{cch} cells. The seeding density was 5000 cells per well. The exponential growth phase (log phase) was initiated on the second day of culture and the plateau phase was reached on the sixth day. Cell number = mean ± SD of six determinations.

cytostatic agent and the magnetic field during 1 h. Table 1 presents experimental data showing the effects of sham exposed, 1 and 25 Hz on drugs' potency over a range of doses from 0.005 to 47.5 μg/ml. Alterations

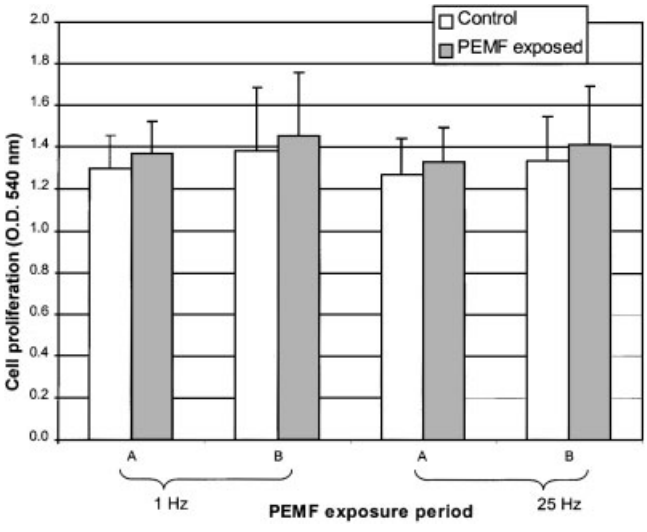

Fig. 5. Effect of magnetic field exposure on cell proliferation of HCA-2/1^{cch} cell line. Mean ± SD of three independent experiments in quadruplicate. (**A**) Exposure to PEMF during 1 h. (**B**) Exposure to PEMF during 2 h/day, for 2 days. Cell proliferation is the number of viable cells measured at 72 h of incubation after PEMF exposure was started for the group A and 48 h for the group B.

caused by PEMF are evidenced by a higher or lower cytotoxicity caused by the drug. The data represents the percentage of survival at different drug doses in relation to control cells without drug.

The response of the cells to the drugs assayed was different, in sham exposed groups, depending on the drug dose. In this way, VCR produced a 40.7 and 19.8% of survival at 4.75 and 47.5 μg/ml; MMC produced a 19.2% of survival at 47.5 μg/ml and cisplatin a 44.2% at 47.5 μg/ml. Nevertheless, lower doses did not produce cytotoxic effect on this cell line.

At 1 Hz, the magnetic field produced alterations in the % of survival for VCR and MMC, exhibiting a 6.1 ($P < 0.01$) and 101.6% ($P < 0.05$) at 47.5 and 0.475 μg/ml, respectively. In contrast, no effect was observed for cisplatin for the dose range assayed.

At 25 Hz, the % of survival obtained for MMC was reduced significantly to 5.3% ($P < 0.001$) at a dose of 47.5 μg/ml (Table 1). Cisplatin showed a 39.1% of survival at 47.5 μg/ml ($P < 0.05$). No significant alteration was obtained for VCR for the doses assayed.

Drug exposure during 1 h and then exposure to PEMF during the next 2 days (2 h/day). The second exposure protocol assayed was the nonsimultaneous exposition of HCA-2/1^{cch} cells to the cytostatic agent and the magnetic field. Therefore, the cell cultures were exposed for 1 h to the cytostatic drug and then drug was removed. Subsequent exposures of the cells to the magnetic field were performed during the next 2 days at a dose of 2 h/day. Table 2 shows the results obtained.

In sham exposed groups, VCR produced a 69.4 and 49.7% of survival at 4.75 and 47.5 μg/ml. For MMC, the % of survival obtained was 37.9 at 4.75 μg/ml and 2.6 at 47.5 μg/ml; and for cisplatin, the % of survival was 24.6% at 47.5 μg/ml.

A significant alteration that reduced the % of survival to 61.5% was obtained for VCR at 4.75 μg/ml, after exposure to 1 Hz ($P < 0.01$).

At 25 Hz, cisplatin reduced the % of survival to 19.7% at 47.5 μg/ml ($P < 0.05$).

No effect was observed for both 1 and 25 Hz for the rest of VCR, MMC, and cisplatin doses (Table 2).

DISCUSSION

VCR, MMC, and cisplatin are anticancer drugs with different mechanisms of action. VCR is an alkaloid that interacts specifically with tubulin, inhibiting its polymerization. MMC is an alkylating agent that forms crosslink with guanine residues, and cisplatin blocks DNA synthesis by crosslinking formation between inter- and intra-DNA strands and between DNA and proteins [Florez et al., 1997].

TABLE 1. Percent Survival of Cells Exposed to Drugs and 1.5 mT Pulsed Electromagnetic Field at the Same Time for 1 h

		Drug dose (μg/ml)				
Drug	EMF exposure	0.005	0.05	0.475	4.75	47.5
VCR	Sham exposed	104.4 ± 4.1	101.5 ± 8.6	101.9 ± 7.7	40.7 ± 6.7	19.8 ± 5.1
	1 Hz	98.9 ± 9.5	92.9 ± 13.7	93.4 ± 8.4	32.9 ± 4.4	6.1 ± 2.2*
	25 Hz	101.6 ± 3.6	101.2 ± 5.2	100.8 ± 3.6	49.6 ± 6.3	19.6 ± 4.3
MMC	Sham exposed	105.4 ± 3.8	106.2 ± 3.1	113.9 ± 5.4	97.8 ± 5.5	19.2 ± 3.2
	1 Hz	100.2 ± 5.9	98.7 ± 5.0	101.6 ± 4.9**	94.0 ± 3.6	24.8 ± 2.7
	25 Hz	102.2 ± 1.1	103.1 ± 0.6	112.6 ± 1.1	84.6 ± 8.8	5.3 ± 1.8***
Cisplatin	Sham exposed	106.1 ± 8.1	103.8 ± 8.2	101.6 ± 10.1	100.2 ± 8.1	44.2 ± 1.3
	1 Hz	101.3 ± 8.8	100.2 ± 7.3	100.5 ± 6.9	103.6 ± 10.5	39.5 ± 3.1
	25 Hz	107.0 ± 7.2	107.7 ± 4.4	104.5 ± 6.9	98.2 ± 6.2	39.1 ± 1.5**

Mean ± SD of four replicates.
*$P < 0.01$.
**$P < 0.05$.
***$P < 0.001$, (Student's *t*-test); in relation to sham exposed cells.

A previous report indicates that HCA-2/1^{cch} cells express P-glycoprotein, which contributes to the resistance to different antineoplastic agents [Ruiz Gómez et al., 2000]. P-glycoprotein is an ATP dependent protein pump in the plasma membrane of multidrug resistant cells, which rapidly removes drugs from the membrane and cytoplasm, preventing a high cytoplasmic concentration, and thus, decreasing cytotoxicity [Kang and Perry, 1994].

In the present study, we evaluated the effects of PEMF on HCA-2/1^{cch}, HCA cells. The growth of these cells incubated in a drug-free medium was not altered by exposure to PEMF. In a previous article, we have reported that cell growth is significantly modified when the parent HCA cells are exposed to the same magnetic fields (1 and 25 Hz, 1.5 mT) [Ruiz Gómez et al., 1999]. This important difference could be influenced by the different exposure times assayed. HCA cells were exposed to PEMF for 15 and 360 min, and HCA-2/1^{cch} cells were exposed to PEMF during 60 and 120 min for 2 days. This difference might be very important to investigate in relation to discern a possible dose–response relationship that could be the aim of future works. This result is in disagreement with the studies reported by Conti et al. [1985], who found a promotion of cell growth exposed to electromagnetic fields. They consider that it had been caused by mobilization of cells in the nonproliferative period of the cell cycle as a result of changes in cell functions, particularly functions of the cell membrane.

A number of articles that show the effects of different field exposures on the uptake and potency of different drugs have been published. In this way, Omote [1988] and Omote et al. [1990] reported that PEMF increases the cell uptake of ^{3}H-methotrexate. They suggest that PEMF promotes the uptake of antitumor agents by cells. In the same way, Liang et al. [1997] have demonstrated that PEMF enhance the potency of

TABLE 2. Percent Survival of Cells Exposed to Drugs for 1 h and Then to 1.5 mT Pulsed Electromagnetic Field for 2 h/Day for the Next 2 Days

		Different drug dose (μg/ml)				
Drug	EMF exposure	0.005	0.05	0.475	4.75	47.5
VCR	Sham exposed	97.9 ± 7.1	94.1 ± 6.7	94.8 ± 6.7	69.4 ± 4.2	49.7 ± 5.9
	1 Hz	92.7 ± 12.2	100.0 ± 5.6	99.1 ± 6.3	61.5 ± 1.9*	43.3 ± 2.6
	25 Hz	97.3 ± 3.6	92.5 ± 2.4	100.1 ± 5.5	63.0 ± 6.5	39.3 ± 4.5
MMC	Sham exposed	99.9 ± 5.4	105.6 ± 2.7	95.8 ± 7.6	37.9 ± 3.3	2.6 ± 0.4
	1 Hz	101.7 ± 4.4	104.1 ± 2.6	96.4 ± 3.5	33.0 ± 4.5	4.1 ± 0.8
	25 Hz	97.4 ± 5.7	102.6 ± 3.4	82.6 ± 6.4	30.5 ± 3.6	2.1 ± 0.2
Cisplatin	Sham exposed	105.1 ± 8.4	103.3 ± 8.6	104.2 ± 7.4	99.3 ± 9.9	24.6 ± 1.4
	1 Hz	101.6 ± 7.5	99.9 ± 5.9	97.3 ± 9.1	96.2 ± 4.7	26.5 ± 2.6
	25 Hz	101.6 ± 6.9	102.2 ± 10.5	100.2 ± 8.8	95.0 ± 7.6	19.7 ± 0.5**

Mean ± SD of four replicates.
*$P < 0.01$ (Student's *t*-test); in relation to sham exposed cells.
**$P < 0.05$.

daunorubicin against the KB-Ch^R-8-5-11 subline when this drug is added before the PEMF exposure. This work is an additional approach to study the effect of PEMF at frequencies below 50/60 Hz.

The data obtained in this report suggest that PEMF exposure (1 and 25 Hz, 1.5 mT peak) can produce alterations in the cytostatic action of VCR, MMC, and cisplatin.

Induced electric fields (E) in the cell culture medium interact initially at the cell membrane. The magnetic field (B), however, penetrates the cell, increasing the possibilities for a biological site of interaction. Magnetic field was not observed to alter the lysosomal function (responsible for dye incorporation) by the exposure [Harland and Liburdy, 1997]. Thus, the magnetic field did not produce alterations in this membrane function. Other authors have suggested that an induced E field associated with microTesla magnetic field strengths may not lead to biological effects [Weaver and Astumian, 1990].

Data shown in this study indicate that PEMF exposure produces more alterations in the cytotoxic effect of drugs when the cells were exposed to PEMF and the cytostatic agent at the same time (Table 1). The results obtained suggest that appropriate drug dose and treatment schedules are important factors for PEMF modulation of cytotoxicity. Our most important observation was that the model cell line HCA-2/1^{cch} responded quite differently in PEMF fields when cotreated with VCR, MMC, or cisplatin. These anticancer drugs kill cells by means of different mechanisms of action; therefore, the increment of drug potency observed in this work could be produced by the interaction of PEMF with molecules or cellular structures related with the normal function of the cell and not directly with the mechanism of drug cytotoxicity. In this way, the study of the function of P-glycoprotein in drug detoxification, tested in different cell lines cotreated with PEMF and cytostatic agents, could be a subject for future work.

This hypothesis has been suggested by other authors, who have used PEMF in the study of the function of P-glycoprotein. Pasquinelli et al. [1993] suggest that this type of magnetic field may inhibit the function of P-glycoprotein and prevent the decrease in the intracellular concentration of the antitumor agent. The potential effect of PEMF at frequencies below 50/60 Hz on this cellular detoxification system is still unclear.

CONCLUSIONS

The data presented in the current report indicate that PEMF can induce modulation of the action of cytostatic agents in the cell line HCA-2/1^{cch}. This could be the result of multifactorial processes influenced by the type of drug, an appropriate dose, the frequency, and the duration of PEMF exposure.

In the future, more studies are needed to clarify the possible biologically based interaction site(s), the influence of all of the above parameters in different cell types and to further determine its potential usefulness in the clinical care.

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