Medical Hypotheses 133 (2019) 109393

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Antitumor effects of the electromagnetic resonant frequencies derived from the ^{1}H NMR spectrum of Ph_3Sn(Mercaptonicotinic)$SnPh_3$ complex

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ARTICLE INFO

Keywords:
Nuclear magnetic resonance
Electromagnetic fields
Leiomyosarcoma
Organotin compounds

ABSTRACT

The aim of this article is to investigate the potential cytotoxic and antitumor effects of the resonant electromagnetic fields (rEMFs) derived from the ^{1}H NMR spectrum of the Ph_3Sn(Mercaptonicotinic)$SnPh_3$ complex (SnMNA). The ability of the complex's rEMFs to induce leiomyosarcoma (LMS) cell death and to recess tumor (leiomyosarcoma) development in Wistar rats was evaluated. The effects of the simultaneous administration of the SnMNA complex at extremely low concentrations and exposure to its rEMFs was also investigated. The emission of the ^{1}H NMR spectrum of the complex alone or in a combination with low ineffective doses of the complex decreased LMS cell viability mainly through apoptosis. Moreover, the results from the *in vivo* experiments showed a significant prolongation of life expectancy in tumor-bearing rats exposed to the rEMFs alongside a deceleration in tumor growth rate. We speculate that the rEMFs of a biologically active substance could exert similar biological effects as the substance itself, mainly when is combined with extremely low ineffective concentrations of the substance.

Introduction

Leiomyosarcoma is a type of soft tissue tumor usually resistant to chemotherapy and irradiation [1]. Cisplatin [cis-diamminedichloroplatinum (II)] and other platinum derivatives are considered as the drug of choice for sarcomas, mainly due to their ability to induce deformation and DNA fragmentation [2].

Besides platinum complexes, many others non-platinum compounds have been developed and tested against various cancer types both *in vitro* and *in vivo* [3]. Increased interest was invested in developing organotin derivatives characterized by potent cytotoxic and anticancer activity [4–8].

Earlier studies investigated the effects of EMFs *in vitro*, *in vivo* and in the clinical setting providing evidence that some of their potential effects are based on electromagnetic resonance principles [9–12]. Subsequent studies revealed that exposure to rEMFs can induce chemical/biological alterations in living organisms such as changes in the antioxidant system, protein levels and Ca^{2+}, Na^{+}, K^{+} ion transfer due to modifications in cellular membrane permeability [13–15]. We have previously published data indicating that coherent rEMFs exert potent cytotoxic and anticancer effects in rat LMS cells and tumors, respectively [16,17]. Recently we have also shown that the rEMFs derived from the ^{1}H NMR spectrum of morphine induce analgesic effects in rats [18].

In the present study we investigated the cytotoxic and antitumor effects of the resonant rEMFs derived from the ^{1}H NMR spectrum of the $\{[(C_6H_5)_3Sn]_2(MNA)\cdot[(CH_3)_2CO]\}$ (SnMNA) complex, on LMS malignant cell line and tumor-bearing Wistar rats and compared them with those of the SnMNA complex itself. Furthermore, the enhanced action between simultaneous administration of SnMNA complex at extremely low, ineffective concentrations and the exposure of LMS to its rEMFs was also studied.

Materials and methods

Electromagnetic field apparatus and exposure conditions

EMFs exposure was performed using the Multi-Channel Dynamic

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https://doi.org/10.1016/j.mehy.2019.109393
Received 28 June 2019; Received in revised form 1 September 2019; Accepted 5 September 2019

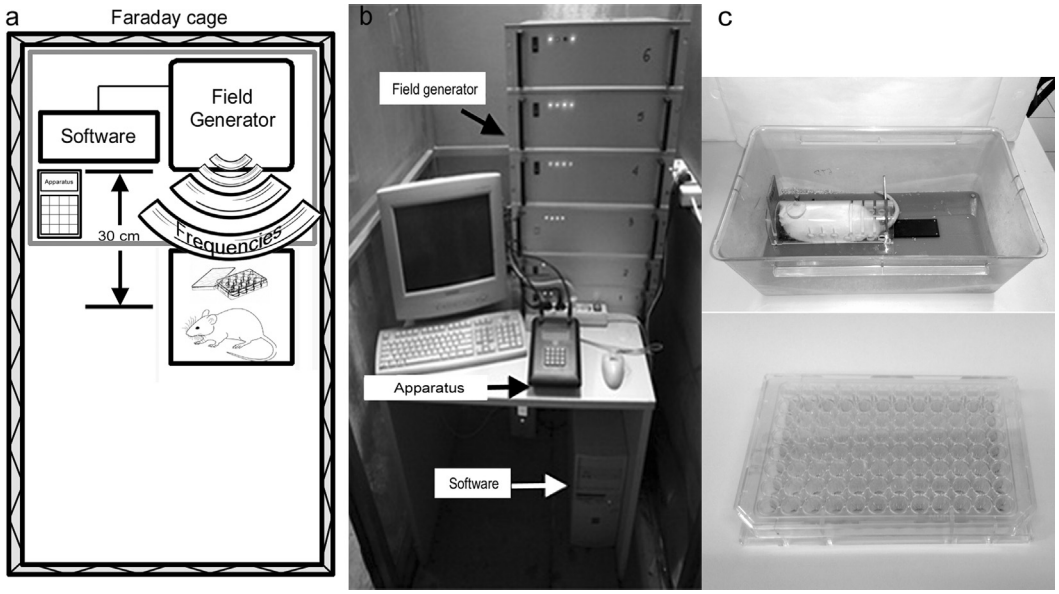

Fig. 1. (a) Schematic presentation of the rEMFs or non-rEMFs emitted from the field generator, (b) the MCDE system in a Faraday cage and (c) the method used to immobilize rats at a distance of 30 cm from the antenna of the MCDE device.

Exciter 100 V1 (MCDE), which was designed and manufactured by K. Havelas and collaborators. The MCDE system was evaluated for its safety application in animal and humans by the Greek National Center for Scientific Research «Demokritos» (Greek Department of the International Committee of Atomic Energy). The MCDE's system technical characteristics according to the technical report of the Greek Atomic Energy Agency [19] are: the intensities for the electrical field are from 1.1 to 1.11 ± 0.01 V/m and for the magnetic field from 0.0027 to 0.0029 ± 0.00005 A/m. The surface power density of the electromagnetic radiation is from 0.00297 to 0.00322 ± 0.00008 W/m^2. This is exactly the power density that is absorbed from the biological targets (cells and rats). The frequencies generated from the MCDE system range from 10 Hz to 1 MHz. The exposures to rEMFs of both *in vitro* and *in vivo* experiments were performed in a Faraday cage in order to avoid interactions with external electromagnetic fields.

Animals and cell cultures were placed at a maximum distance of 30 cm from the antenna of the MCDE device in order to get the same rate of energy transfer per unit area (power density) as it is transferred from the antenna and to provide a uniform distribution to the resonant and non-resonant electromagnetic fields, emitted from the apparatus (Fig. 1a and b). Rats were immobilized inside a restrainer enclosed by plexiglas walls to keep the distance constant at 30 cm (Fig. 1c).

NMR transformation to resonant radiofrequencies

The elemental analysis ^{1}H NMR for SnMNA complex is shown in Fig. 2 [20]. The equation used to calculate the rEMFS from the chemical shift (ppm) of the SnMNA ^{1}H NMR was: rEMFs (Hz) = chemical shift (ppm) × 250 MHz (fundamental frequency of the spectrophotometer) [21].

A total of 22 resonant frequencies, resulted after the appropriate transformation, were used as the group of rEMFs (Table 1). As a control group, we used). a group of 22 non-resonant frequencies (non-rEMFs) possessing the same energy to that of the rEMFs (Table 1).

In vitro studies

Leiomyosarcoma cell culture

The LMS cells were isolated from selected leiomyosarcoma tumors of Wistar rats, which were developed after benzo(a)pyrene induction, as it has previously been described [16,17].

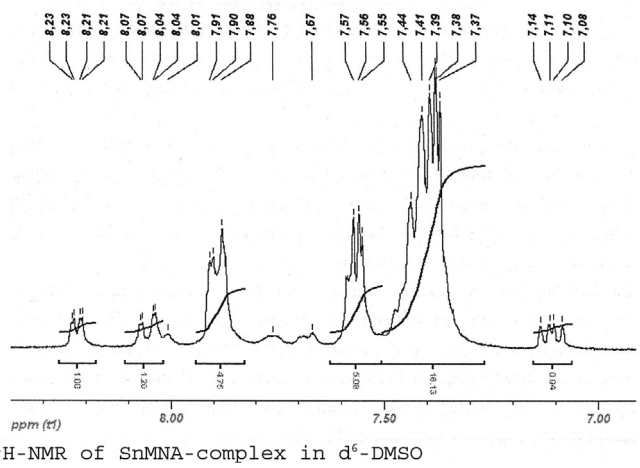

Fig. 2. ^{1}H NMR analysis of the SnMNA-complex in d^6-DMSO.

SnMNA complex

The triorganotin compound bis[triphenyltin(IV)](3-carboxy-pyridine-2-thionato) (SnMNA) was synthesized as previously described [22,23].

Exposure of the LMS cells to the coherent rEMFs of the SnMNA complex

The LMS cells were placed in a Faraday cage inside an incubator chamber and irradiated with the rEMFs for 45 min, 120 min, and 300 min per day for two consecutive days. The same mode of exposure was also applied in LMS cells with the non-rEMFs. rEMFs Furthermore, in order to study the potential enhanced effects of the SnMNA complex and exposure to its rEMFs, LMS cells were treated with low, ineffective concentrations (10^{-12}, 10^{-15} and 10^{-18} M) of the SnMNA complex for 2–3 h before their exposure to the rEMFs. Also, LMS cells exposed to a randomly selected non-rEMFs.

Cell survival

LMS cells were seeded in 96-well plates at a density of 5×10^3 cells per well for 24 h before exposure to the rEMFs or non-rEMFs. The survival of LMS cells was estimated using the MTT (3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide) assay. Briefly,

Table 1
The peak resonant frequencies of SnMNA's ^{1}H NMR and the group of non-resonant frequencies used in the study.

Number of frequencies	Peak from ^{1}H NMR spectrum (ppm)	Resonant frequencies (Hz)	Non-Resonant[#] frequencies (Hz)*
1	7.08	1770	1500
2	7.10	1775	1507
3	7.11	1778	1534
4	7.14	1785	1559
5	7.37	1843	1586
6	7.38	1845	1614
7	7.39	1848	1632
8	7.41	1853	1652
9	7.44	1860	1687
10	7.55	1888	1701
11	7.56	1890	1713
12	7.57	1893	2092
13	7.67	1918	2103
14	7.76	1940	2135
15	7.88	1970	2159
16	7.90	1975	2179
17	7.91	1978	2199
18	8.01	2003	2218
19	8.04	2010	2251
20	8.07	2018	2284
21	8.21	2053	2309
22	8.23	2058	2337

[#] The 22 non-resonant frequencies consisted of frequencies above and below the resonant spectrum of the complex carried the same energy as the rEMFs.

the cells were incubated with 50 µl of MTT (stock solution of 3 mg/ml) for 3 h. Then, the medium was removed and the formed blue formazans were diluted in 200 µl of DMSO. Absorbance was determined at 540 nm (background absorbance measured at 690 nm) using a microplate spectrophotometer (Multiskan Spectrum, Therno Fisher Scientific, Waltham, USA). All experiments were performed in triplicates. Data of each set of experiments after exposure to rEMFs or non-rEMFs for a specific time period were expressed as % relative cell proliferation compared to control.

Quantification of apoptosis

LMS cells (60×10^3 cells/ml) were incubated for 24 h in 6-well plates before the addition of the SnMNA complex and/or exposure to the rEMFs or non-rEMFs. At the end of the treatment, the cells were collected, counted and 10^6 cells were suspended in 1 ml of cold calcium binding medium Annexin V-FITC (5 µl) and propidium iodide (PI) (4 µl) were added and left for 30 min in the dark at room temperature.min Levels of apoptosis were quantified by flow cytometry (CyFlowML, Partec, Munster, Germany). Percentage of apoptotic and necrotic cells was calculated on overall viable cells (100%).

Cell cycle analysis

LMS cells (60×10^3 cells/ml) were incubated for 24 h in 6-well plates before the treatment with the SnMNA and/or exposure to the rEMFs or non-rEMFs. After 48 h, cells were harvested and centrifuged for 5 min at 3500 rpm. The cell pellet was resuspended in ice-cold 70% ethanol for 10 min, washed with PBS and then incubated with 50 µl RNase A (100 µg/ml) at room temperature, for 10 min. After 15 min staining with 50 µg/ml PI in the dark at room temperature, the samples were analyzed by flow cytometry (CyFlowML, Partec, Munster, Germany).

In vivo studies

Forty female Wistar rats, aged 2–3 months and weighing 190 ± 15 g, were used in this study. The rats were housed in community cages at controlled room temperature (20 ± 2 °C), and lighting (12 h light/12 h dark) and had *ad libitum* access to a standard chow diet and water.

Experiments on animals were handled with human care in accordance with the European Union directive for the care and the use of laboratory animals (EEC Directive 2010/63/EU) and according to the permission number 20EEP02. Induction of leiomyosarcoma tumors in Wistar rats performed by inoculation of leiomyosarcoma cells at their dorsal area, as previously described [8]. Palpable tumors were observed 12 d after inoculation.

Exposure time to the rEMFs or the non-rEMFs of the complex was set at 5 h every day for 21 consecutive days (until the day that the first animal in the control group died). The animals were observed for their behavior once a day.

The rats were randomly divided into 4 groups (10 animals per group) as follow a) exposure to the 22 rEMFs of the complex (rEMFs group); b) intraperitoneal administration of a low, ineffective dose (5.4 ng/kg BW once per week) of the SnMNA complex (LD-SnMNA group); c) intraperitoneal administration of the ineffective dose of the SnMNA complex (similar to LD-SnMNA) and simultaneous exposure to the complex's rEMFs (similar to rEMFs) (Combination group) and d) exposure to randomly selected non-rEMFs (Non-rEMFs group).

Animals were euthanized and tumors were carefully removed and weighted. The mean survival time (MST, the period of time from the diagnosis of tumor development until the death of the animal), the mean tumor weight ((MTW, the weight of the tumor at death (g))) and the mean tumor growth rate ((MTGR, equal to the tumor weight (g) at death divided by the survival time (days))) were calculated.

Statistical analysis

Data are expressed as mean ± S.D. The statistically significant difference between data means was determined by Student's *t*-test and two-way analysis of variance (ANOVA) was used for statistical evaluation of differences between groups (SPSS version 16.0, Statistical Package for the social Sciences software, SPSS, Chicago). p-values < 0.05 were considered as significant.

Results

In vitro studies

The treatment with the low concentrations of the SnMNA complex was found ineffective as well as the exposure of the cells to the non-rEMFs of the complex (Fig. 3A–C). Exposure of the LMS cells to the rEMFs for 45 min for 2 d consecutively with or without the simultaneous treatment of the SnMNA at the low concentrations had no significant cytotoxic effects (Fig. 3A). Increasing the exposure time to 120 min and 300 min (for 2 d as well) resulted in a significant inhibition of cell viability, corresponding to a decreased cell number by 9% and 32%, respectively ($p < 0.05$). Simultaneous treatment with the extremely low concentrations of the SnMNA and exposure to its rEMFs showed significant enhancement of the cytotoxic effects that were maximized at the lowest concentration of 10^{-18} M. Specifically, the LMS cells viability was reduced by 17% and 21% compared to the cells exposed only to the rEMFs for 2×120 and 2×300 min, respectively (Fig. 3A–C).

Analysis of the levels of apoptosis by flow cytometry revealed that LMS cells treated with 10^{-15} and 10^{-18} M of the SnMNA complex and simultaneously exposed to 2×300 min of rEMFs showed a significant increase in apoptosis by 6 and 8%, respectively. There was no difference in apoptosis at the 2×120 min treatment group (Fig. 4). Furthermore, SnMNA treatment alone or in combination with its rEMFs had no impact on the cell cycle, analyzed by flow cytometry (Table 2).

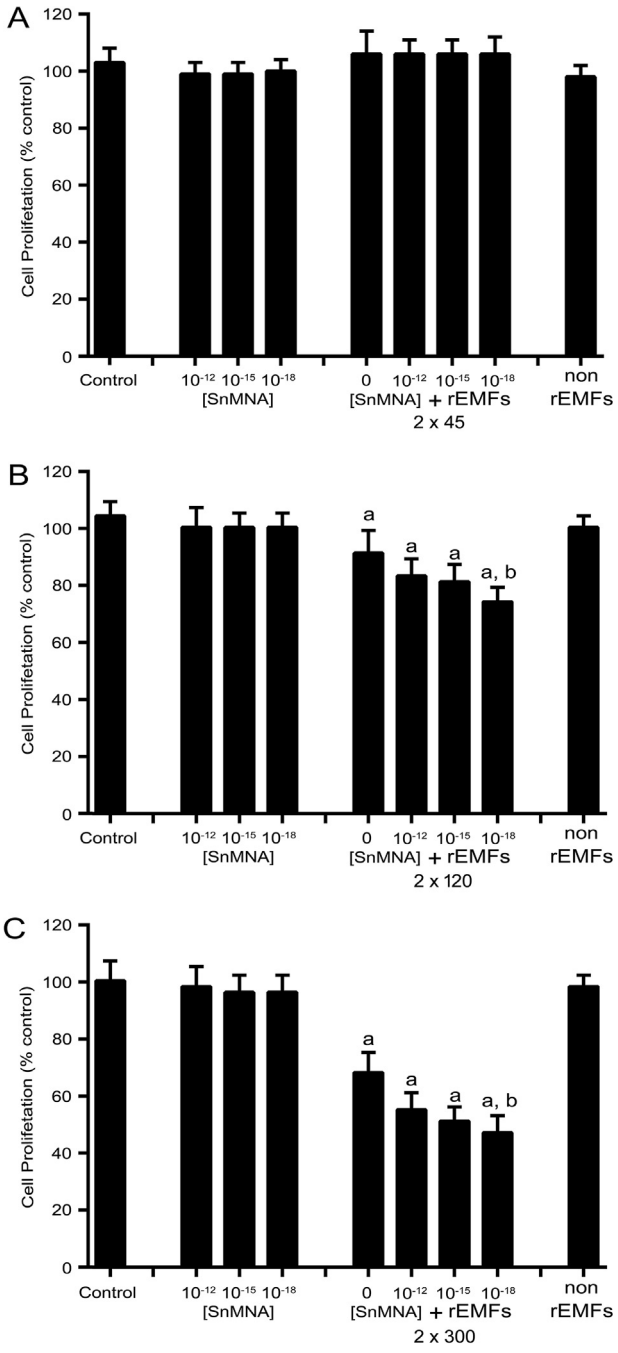

Fig. 3. LMS cells viability after exposure to the rEMFs of the SnMNA complex for 2d × 45 min (A), 2d × 120 min (B) and 2d × 300 min (C) alone and with the addition of the complex at extremely low concentrations (10^{-12}, 10^{-15} and 10^{-18} M). [a]Statistically significant different from the Control, $p < 0.05$; [b]Statistically significantly different from cells exposed to the rEMFs without the addition of the complex, $p < 0.05$.

In vivo studies

The treatment of tumor-bearing rats with the SnMNA complex significantly prolongs the survival time (2× fold increase) and decelerates the tumor growth rate (more than 70% reduction), compared to untreated tumor-bearing rats, as we have previously shown (Table 3) [8]. Rats of the rEMFs and Combination Group presented a significant prolongation in life expectancy compared to the CG (1.6× and 1.8× fold increase, respectively) (Table 3). The MTGR in animals of rEMFs and Combination Group was lower than the control ($p < 0.05$), the LD-SnMNA ($p < 0.05$) and the non-rEMFs groups ($p < 0.05$) but still higher than the SnMNA group ($p < 0.05$). The slower tumor growth rate in rEMFs and Combination Group allowed the animals to live longer than the Non-rEMFs and LD-SnMNA animals, but the tumors were bigger at the time of death. On the other hand, exposure of rats to the non-rEMFs had no beneficial antitumor effect (Table 3 and Fig. 5).

Discussion

Exposure of LMS cells to the resonant frequencies of the SnMNA complex significantly reduced cell viability and increased apoptosis, compared to the control group. The best cytotoxic and apoptotic effects were shown in cell cultures treated with ineffective doses of SnMNA complex and simultaneously irradiated with the rEMFs of the complex. No effects were recorded in cell cultures irradiated with the non-resonant EMFs.

Exposure of tumor-bearing rats to the rEMFs of the SnMNA complex, significantly prolonged their life expectancy (survival time) and lowering the MTGR. Furthermore, the best antitumor effects were shown in animals from the Combination Group, treated with low, ineffective doses of SnMNA (5.4 ng/kg BW) and simultaneously exposed to the rEMFs of the complex. On the contrary, exposure of both LMS cells and tumor-bearing animals to non-rEMFs, possessing the same energy to the rEMFs, had no effects, indicating that the rEMFs of the complex seem to exert a more targeted phenotype.

Although, several possible explanations have been proposed so far to address and explain the possible cellular effects of EMFs on biological systems the mechanisms remain still unclear. *In vivo* experiments provide evidence for the ability of the electromagnetic radiation (extremely low-frequency electromagnetic fields) to suppress the tumor vascularization [24,25] by affecting the vascular endothelial growth factor signal transduction pathway [25]. In our study, the effects of the SnMNA rEMFs on malignant cells and tumor-bearing rats could be attributed to the suppression of cell viability and the induction of apoptosis, since no significant alterations were recorded on the cell cycle analysis. The mechanism of action of the SnMNA complex itself (on malignant cells *in vitro* and leiomyosarcoma-bearing animals) has been previously investigated [8,22,23]. It was shown that the complex induces high apoptosis on the LMS cells at very low concentrations (20 nM) [8]. Some of its cytotoxic effects can also be attributed to the metabolic actions of the nicotinic acid of the complex or to the inhibitory effects of the SnMNA-complex on 5-lipoxygenase [26]. We speculate that the specific energy emitted by the SnMNA-rEMFs could stimulate the production of free radicals, resulting in high cytotoxic effects. It was recently shown that the production of reactive oxygen species is increased when cancer cells (originating from lung, head and neck, colorectal and pancreas) are exposed to low-dose electromagnetic fields (EMF) leading to DNA fragmentation and inhibition of cell proliferation [27]. Induction of apoptosis by EMFs could also be provoked by the alteration of T-type Ca^{2+} channel permeability which also leads to the disruption of cell proliferation [28] or by the elevation of caspase-3 [29].

We have shown that the combination of low, ineffective doses of SnMNA with its rEMFs presented significantly higher cytotoxicity, apoptosis as well as prolongation of the survival time of tumor-bearing rats. Even though the results are clear and potent in both *in vitro* and *in vivo* models, the mechanism remains unknown.

Previous studies have also shown that electronic transmission of thyroxine on frogs seems to induce the same effects as thyroxin itself [30]. According to Thomas *et al* signals derived from phorbol myristate acetate and transmitted electronically on human neutrophils induce the production of free radicals similar to those of the administration of the substance itself [31]. Moreover, Tsong *et al* showed that electromagnetic signals of defined frequency and amplitude can be absorbed by cell membranes offering energy to ATPases and using it to perform chemical work [32]. Recently, Maniati *et al* showed that odorant

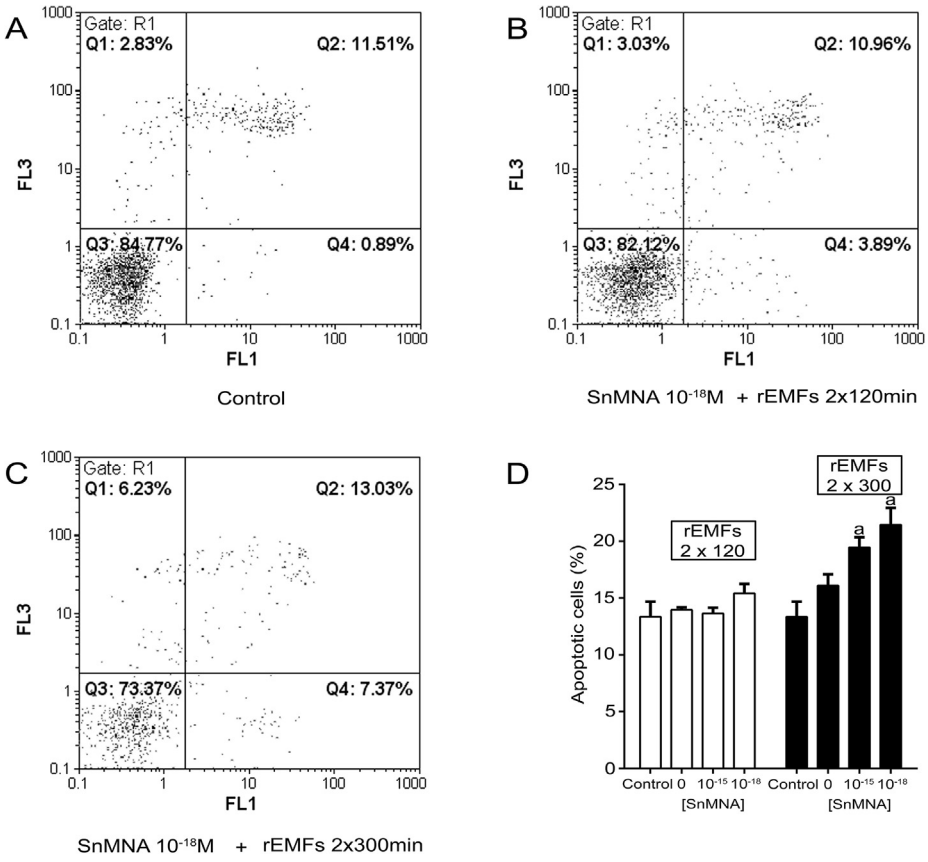

Fig. 4. Apoptotic effects induced by exposure of the LMS cells to the rEMFs of the SnMNA complex for 2d × d 120 min and 2dd × 300 min alone and with the addition of the complex at extremely low concentrations (10^{-15} and 10^{-18} M) (Fig. 3D). A–C are representative plots of the control, the exposure of cells to the rEMFs for 2d × d 120 min with the addition of the complex at an extremely low concentration (10^{-18}) and the exposure of cells to the rEMFs for 2d × d 300 min with the addition of the complex at an extremely low concentration (10^{-18}), respectively. [a]Statistically significant different from the Control, $p < 0.05$.

Table 2
Quantification of cell cycle phases after the exposure of the cells to the rEMFs of the SnMNA complex.

	G0/G1	S	G2/M	SubG1
Control	61.8 ± 3.1	16.4 ± 2.3	15.9 ± 1.6	5.9 ± 0.9
rEMFs 120 min	59.0 ± 2.9	15.2 ± 2.7	18.9 ± 1.4	6.9 ± 0.8
rEMFs 120 min + SnMNA 10^{-18} M	59.0 ± 2.5	15.7 ± 2.3	19.0 ± 1.2	6.3 ± 0.7
rEMFs 300 min	58.6 ± 2.8	17.1 ± 2.9	18.7 ± 1.5	5.7 ± 1.0
rEMFs 300 min + SnMNA 10^{-18} M	58.7 ± 3.2	16.0 ± 2.1	17.8 ± 1.8	7.6 ± 1.2

Table 3
Antitumor activity of the SnMNA and its rEMFs against tumor bearing Wistar rats.

Groups	MST (days)			MTW (g)	MTGR (g/day)
	Mean	Min	Max		
rEMFs	38.1 ± 10.9[a,b,c]	22	52	76.8 ± 7.0	2.2 ± 0.7[a,b,c,d]
LD-SnMNA	23.5 ± 4.5	17	31	68.7 ± 5.9	3.0 ± 0.6
Combination	42.1 ± 12.9[a,b,c]	25	58	75.9 ± 15.5	2.0 ± 0.8[a,b,c,d]
Non rEMFs	23.3 ± 5.2	16	32	67.9 ± 4.7	3.0 ± 0.7

[a]$p < 0.05$ vs control; [b]$p < 0.05$ vs LD-SnMNA; [c]$p < 0.05$ vs non rEMFs; [d]$p < 0.05$ vs SnMNA.

molecules possess vibrational frequencies by which, each one, react with a single receptor of Drosophila melanogaster's olfactory system [33]. We have also shown that exposure of rats to the electromagnetic resonant frequencies derived from the ^{1}H NMR spectrum of morphine induces analgesic effects, acting probably through morphine receptors [18].

The above-mentioned data in addition to the ones reported in the present study indicate that the biological effects, of a chemically active compound may be "conserved" to the various types of its resonant electromagnetic frequencies and exert on biological systems similar effects as the compound itself. The potent biological effects are shown in the combination group along with the absence of side effects, renders this methodology unique, with high expectations, in terms of biological applications, but still needs to be examined for its efficacy and reproducibility in many other biological systems by using the resonant frequencies of appropriate molecules.

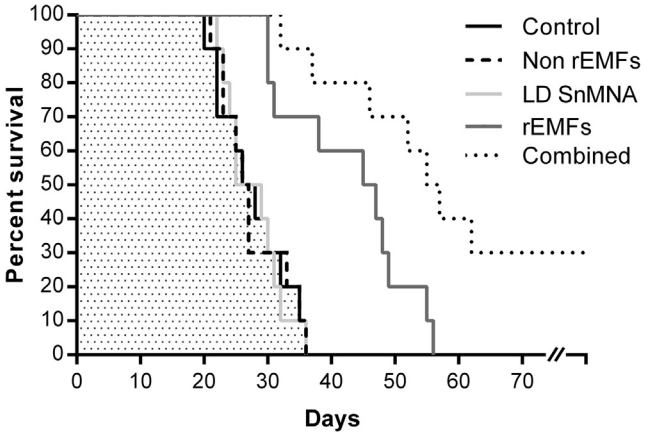

Fig. 5. Survival curve for animals of the Control, Combination, rEMFs, non-rEMFs and LD-SnMNA groups.

Grant

This work is supported by development funds from the Department of Physiology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.109393.

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