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Lack of promotion of 7,12-dimethylbenz[*a*]anthracene-initiated mouse skin carcinogenesis by 1.5 GHz electromagnetic near fields

Katsumi Imaida[1,3,4], Kazuya Kuzutani[1], Jianqing Wang[2], Osamu Fujiwara[2], Tadashi Ogiso[1], Koji Kato[1] and Tomoyuki Shirai[1]

[1]1st Department of Pathology, Nagoya City University Medical School, 1-Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601 and [2]Department of Electrical and Computer Engineering, Nagoya Institute of Technology, Gokiso-cho, Showa-ku, Nagoya 466-8555, Japan

[4]Present address: Department of Pathology, Kagawa Medical University, 1750-1 IKENOBE, Miki-cho, Kida-gun, Kagawa 761-0793, Japan

[3]To whom correspondence should be addressed

The effects of 1.5 GHz electromagnetic near fields of time division multiple access (TDMA) signal for the Personal Digital Cellular, Japanese cellular telephone standard (PDC) used for cellular phones, on mouse skin carcinogenesis initiated by 7,12-dimethylbenz[*a*]anthracene (DMBA) were examined. Ten-week-old ICR female mice were treated with a single application of DMBA on shaved dorsal skin by painting at a concentration of 100 μg/100 μl acetone per mouse. One week later, mice were divided into four groups, receiving electromagnetic near fields exposure (DMBA–EMF), sham-exposure (DMBA–Sham), 12-*O*-tetradecanoylphorbol-13-acetate (TPA, 4 μg /200 μl acetone/mouse), as a positive control (DMBA–TPA), and no-treatment (DMBA–Control). EMF near fields exposure conditions were as follows: skin local peak specific absorption rate (SAR) 2.0 W/kg, whole body average SAR 0.084 W/kg (ratio of peak to average SAR is 24), 90 min a day, 5 days a week, for 19 weeks. At week 20, animals were killed and skin tumors were analyzed histopathologically. The incidences of skin tumors in DMBA–EMF, DMBA–Sham, DMBA–TPA and DMBA–Control groups were 0/48 (0%), 0/48 (0%), 29/30 (96.6%) and 1/30 (3.3%), respectively. Histopathologically, papilloma and squamous cell carcinoma (SCC) were observed in the DMBA–TPA group and only papilloma observed in the DMBA–Control group. The incidences of squamous cell papillomas and squamous cell carcinomas in DMBA–TPA and DMBA–Control groups were 29/30 (96.6%) and 1/30 (3.3%), respectively, numbers of tumors per mouse (tumor multiplicity) being 18.8 ± 13.4 and 0.1 ± 0.5. These data clearly demonstrated that near fields exposure to 1.5 GHz EMF, used for cellular phones, does not exert any enhancing effect on skin tumorigenesis initiated by DMBA.

Introduction

The use of cellular phones has been spreading rapidly in not only developed countries but also in the developing world. Although the potential risk to human health from antenna electromagnetic fields, especially with respect to brain tumors, leukemia and mammary gland neoplasia has been a source of great concern, no actual danger has been confirmed so far.

We have already reported lack of effects of local body exposure to 929.2 MHz electromagnetic fields (EMF)(1) or 1.439 GHz EMF (2) on rat liver carcinogenesis using a medium-term liver bioassay system for carcinogens (3–8), in which glutathione *S*-transferase placental form (GST-P) positive liver foci, preneoplastic rat liver lesions, were used as endpoint markers. Thus time division multiple access (TDMA) signals for the Personal Digital Cellular, Japanese cellular telephone standard (PDC), did not enhance the development of liver lesions. However, serum hormonal levels of ACTH, corticosterone and melatonin were affected by EMF exposure.

With use of cellular phones, EMF would be expected to affect directly the skin of the ears and head, as well as internal organs, such as the brain. Therefore, in the present experiment, we focused on the skin, as a target of EMF exposure, employing a 7,12-dimethylbenz[*a*]anthracene (DMBA) mouse skin carcinogenesis model. The effects of low magnetic fields (60 Hz) exposure on mouse skin carcinogenesis have already been reported, with no tumor promotion (9,10) or co-promotion with 12-*O*-tetradecanoylphorbol-13-acetate (TPA) (11). However, to our knowledge, the effects of 1.5 GHz EMF using cellular phones on skin carcinogenesis have hitherto not been reported.

Abbreviations: DMBA, 7,12-dimethylbenz[*a*]anthracene; ELFs, extremely low frequency magnetic fields; EMF, electromagnetic fields; PDC, Personal Digital Cellular; SAR, specific absorption rate; SCC, squamous cell carcinoma; RFs, radio frequency fields; TDMA, time division multiple access; TPA, 12-*O*-tetradecanoylphorbol-13-acetate.

Materials and methods

The exposure apparatus was specially designed for this study (12). 1.49 GHz electromagnetic near fields of TDMA signals for the PDC system (50 pulses per second with a duty ratio of 33%) was directed at mouse skin through an electrically short mono-pole antenna with capacitive-loading, which realizes highly localized peak specific absorption rates (SARs) on skin above 2.0 W/kg, with a whole body-averaged SAR below 0.084 W/kg for mice.

The temporal homogeneity of the exposures was evaluated by measuring the temporal variation of the antenna output power, which was derived from the difference between the incident power to the antenna and the reflected power from the antenna. Measurements were made for six mice of different weights, with a two-channel power meter and the data from the power meter were recorded in a 1 sec interval. The result indicated that during the 90 min exposure period, the temporal variations of the antenna output power were within ±7%.

Homogeneity of the EM field between mice was evaluated by measuring the field strength beneath the antenna, for each exposure box, with the mouse removed (measurement inside living mice is very difficult). It was found that the field strength in the 48 exposure boxes ranged from –5% to +3% with respect to the designed value.

Due to the near-field exposure characteristics, the field strength in the initiated skin surface area was not uniform. The computer simulation results showed that the field strength in this area varied within 10%.

Figure 1 shows a diagram of the exposure apparatus used in the present study. Exposure lasted 90 min a day, 5 days a week, for 19 weeks. Durations of exposure per day (90 min) and per week (5 days) were based on the previously reported animal experiments of radio frequency animal carcinogenesis studies (1,2).

Figure 2 shows the protocol for this study of mouse skin carcinogenesis. It was approved by the Animal Care Committee of Nagoya City University

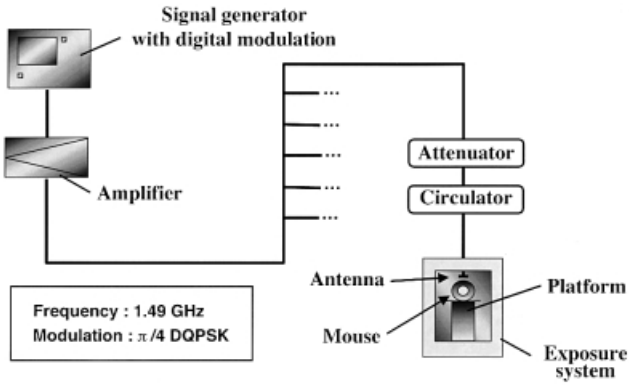

Fig. 1. Block diagram of EMF exposure apparatus.

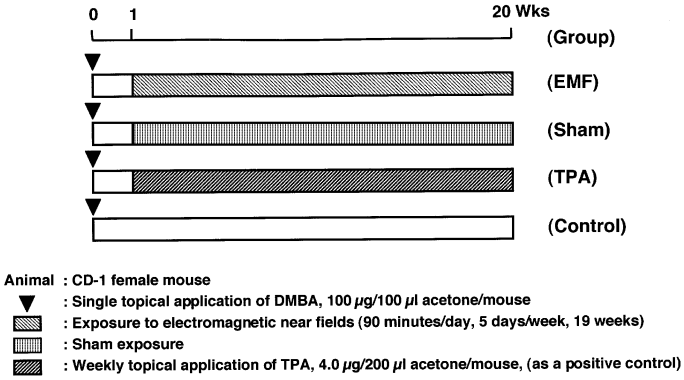

Fig. 2. Experimental protocol for the effects of 1.5 GH_8 electromagnetic near field on mouse carcinogenesis.

Medical School. CD-1 female mice (Charles River Japan, Atsugi) at 9 weeks of age were housed, five per cage with wood-chip bedding, in an air-conditioned specific pathogen free (SPF) animal room at 24 ± 2°C and 55 ± 5% humidity, with a 12 h light–dark cycle. At the age of 10 weeks, all mice were subjected to topical application of DMBA on pre-shaved dorsal skin by painting at a concentration of 100 μg/100 μl acetone per mouse. One week later, mice were divided into four groups. Animals in group 1 were then exposed to EMF (DMBA–EMF group). Each mouse was held in a plastic cylinder, just fitting to the body, with a slit at the top and the bottom, and several holes on both sides for air ventilation. The slit open at the top of the cylinder, allowed a separation of only ~3 mm between mouse skin and the antenna.

Each mouse was exposed in an individual exposure box. The exposure box is made of aluminum, and its insides, except for the roof and the front door, are inlaid with planar rubber ferrite absorber that has a reflection loss of at least 21.8 dB at 1.5 GHz. The roof of the box acts as the ground for a capacitive-loading mono-pole antenna which is fed at the center of the roof. The capacitive-loading monopole antenna was realized with a metal circular plate having a diameter of 7 mm and a thickness of 1 mm attached to the tip of a 1/8-wavelength mono-pole element. The front door is a new type of transparent absorber (developed by TDK, Japan) and it is able to supply a reflection loss of 20 dB. Since the peak SAR varies drastically with the distance between the mouse and the antenna, an acrylic holder was set on a plastic platform to restrain the mouse so that its dorsum was positioned just beneath the capacitive-loading monopole antenna.

Forty-eight exposure boxes (24 for EMF exposure and 24 for sham exposure) were employed. Animals in group 2 were placed in the same cylinders in the exposure boxes in the same manner, but without actual exposure to EMF (DMBA–Sham). Animals in group 3 received weekly topical applications of TPA (4.0 μg /200 μl acetone/mouse) as a positive control (DMBA–TPA). Animals in group 4 were treated with DMBA alone and were served as a carcinogen control group (DMBA–Control). All skin tumors detected were recorded and counted every week along with body weights. At week 20, animals were anesthetized with ether and blood samples were collected from the aorta (for hormonal analysis) from five mice in each group before they were sacrificed. The blood sample collection was performed around 9:30AM to 10:30AM. The dorsal skins were excised, placed on flat paper and fixed in buffered formalin solution. The following organs were weighed at autopsy and histopathologically analyzed: liver, kidney, adrenal glands and spleen. The thickness of dermis was measured by image analyzer (IPAP; Image Processor for Analytical Pathology, Sumika Technoservice, Osaka, Japan). Serum levels of corticosterone and adrenocorticotropic hormone (ACTH) were measured at SRL, Tachikawa, Japan, by radioimmunoassay. Melatonin was also measured at SRL, by a double-antibody radioimmunoassay method with the Kennaway G280 anti-melatonin antibody (13).

Statistical analyses were carried out using the Student's *t*- or Welch's *t*-test after application of the preliminary *F*-test for equal variance.

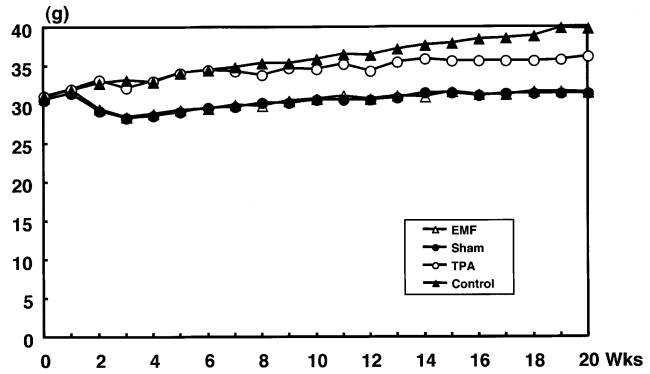

Fig. 3. Growth curves of mice treated with DMBA followed by 1.5 GH_8 EMF exposure or TPA treatment.

Results

Decreases in the body weights were observed in the DMBA–EMF and DMBA–Sham groups after week 2 of the experiment, following commencement of restraint in mouse holders. However, no statistically significant differences were observed between the two groups (Figure 3). Retardation in body weight gain was also observed in the DMBA–TPA group, compared with the DMBA–Control group.

Skin tumors were macroscopically detected in the DMBA–TPA group (group 3) from week 6 until the termination of the experiment. Numbers of skin tumors per mouse are shown in Figure 4. At the end of the experiment, 18.8 tumors per mouse were observed in the DMBA–TPA group. However, there were no skin tumors in the DMBA–EMF (group 1) or DMBA–Sham (group 2) groups, throughout the experiment.

Table I summarizes the histopathological findings for skin tumors. All were classified as squamous cell papillomas or squamous cell carcinomas (SCC), most being benign papillomas with only two SCCs in the DMBA–TPA group (group 3). Incidences and numbers of tumors per mouse in the DMBA–TPA and DMBA–Control groups were as follows: 29/30 (96.6%) and 18.8; 1/30(3.3%) and 0.1, respectively. No skin tumors were detected in either the DMBA–EMF or DMBA–Sham groups (groups 1 and 2), histopathologically.

Table II summarizes data for the thickness of the epidermis of dorsal skin of mice treated with DMBA followed by EMF exposure. Average values were 11.8, 12.4 and 12.5 μm for the DMBA–EMF, DMBA–Sham and DMBA–Control groups, respectively, with no statistically significant intergroup differences.

Lymphomas/leukemias were developed in the liver and/or the kidney of all groups (Table III). Incidences were between 4.2% to 16.7%, with no significant differences between groups.

Data for serum hormonal levels are summarized in Table IV, no intergroup variation being evident for melatonin, corticosterone or ACTH.

Table I. Incidences and multiplicity data for skin tumors in treated mice

Group	No. of mice	Incidence (%)			Multiplicity (No./mouse)
		Papilloma	Carcinoma	Total	
DMBA→EMF	48	0 (0)	0 (0)	0 (0)	0
DMBA→Sham	48	0 (0)	0 (0)	0 (0)	0
DMBA→TPA	30	29 (96.6)***	2 (6.7)	29 (96.6)***	18.8 ± 13.4***
DMBA→Control	30	1 (3.3)	0 (0)	1 (3.3)	0.1 ± 0.5

***$P < 0.001$ vs DMBA → Control group.

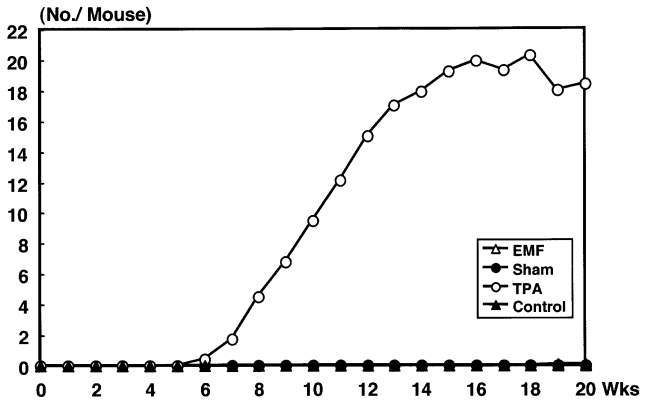

Fig. 4. Numbers of macroscopically detected skin tumors observed on mouse skin (numbers of tumors/mouse).

Table II. Thickness of epidermis of back skin of mice treated with DMBA followed by EMF exposure

Group	No. of mice	Thickness (μm)
DMBA→EMF	10	11.82 ± 1.01[a]
DMBA→Sham	10	12.40 ± 1.21
DMBA→Control	10	12.47 ± 1.45

[a]Mean ±SD.

Discussion

The present investigation of the biological effects of 1.5 GHz near fields of EMF in a DMBA-mouse skin carcinogenesis model of 20 weeks experimental duration revealed no promoting influence. Since this model has been widely used as a tool for investigation of modifying potential (14,15), it can be said to be an appropriate assessment of EMF exposure. In addition, 48 animals were used for EMF and sham exposure groups, this being a sufficient number of animals for the detection of minimal changes in mouse skin tumor development. Although few or no skin tumors in the DMBA–Sham or DMBA–Control groups were observed, skin tumors in the DMBA–TPA, the positive control group, were observed in 96.6% animals as expected. Therefore, their lack in both the DMBA–EMF and DMBA–Sham groups, indicates that EMF exposure did not exert any promoting potential on mouse skin carcinogenesis.

In the present experiment, since the distance between the skin and the antenna was a very important factor for the achievement of 'near fields exposure', a specific size of mouse had to be held in a plastic mouse holder, specifically designed for the experiment. Therefore, 10-week-old mice were used at the beginning of the experiment. In our previous experiment regarding EMF exposure and rat liver carcinogenesis (1,2), stress hormones, such as ACTH and corticosterone were influenced, but there were no significant differences among experimental groups in the present study (Table IV). These data suggest that mice may be more tolerant to the stress encountered than rats.

Melatonin is a hormone produced by the pineal gland. Several reports have been published regarding relationships between serum melatonin levels and carcinogenesis, such as in the mammary gland (16–18), and colon (19). Melatonin is also reported to modulate cell proliferation (20,21), and intercellular junctional communication in MCF-7 human breast cancer cells (22). While EMF may depress melatonin production (23,24), and enhance rat mammary tumorigenesis (25,26), our previous rat medium term liver bioassay of EMF effects demonstrated elevated melatonin levels and the numbers and areas of the preneoplastic liver foci (GST-P) had a tendency to decrease (1,2). Furthermore, our additional study of exogenous melatonin treatment in the same animal model revealed decrease in GST-P positive foci development (27). While no effects on melatonin levels were found, melatonin was sampled during light hours when such an effect may not be seen. In the present study, serum levels of melatonin did not significantly differ among the groups, but in the CD-1 female mouse they are known to be much less than in F344 male rats (2). Hence, this species difference could have exerted a complicating influence.

Regarding dosimetry of EMF exposure to the mouse skin, the skin peak SAR was 2.0 W/kg and mean body SAR was 0.08 W/kg (12). The ratio of the average body SAR to the skin peak SAR was sufficiently high that any effect of body heating by the exposure could be ignored.

Several epidemiological investigations have suggested an increased incidence of lymphoma, leukemia and mammary tumors in residents living near power transmission lines (28). However, some observers failed to confirm such a positive correlation (29). Although the observations were for extremely low frequency magnetic fields (ELFs), effects of radio frequency fields (RFs), such as those used for cellular phones, on the same malignancies have also given rise to concern (30). In the present study, lymphoma/leukemia was induced by topical application of DMBA treatment, but the incidence was not affected by the EMF exposure.

Sunburn is a major factor for human skin cancer especially for white people (31), and avoidance of excessive exposure to UV light is therefore recommended. Since UV light also has electromagnetic fields, combined effects of both UV light and EMF exposure on skin carcinogenesis may be an important subject for future investigation.

In terms of the effects of EMF on brain tumorigenesis, a long-term rat study of 1.5 GHz near field exposure to rats,

Table III. Incidences of lymphomas/leukemias in mice treated with DMBA followed by EMF exposure or TPA treatment

Group	No. of mice	No. of mice observed in		Total no. of mice bearing lymphomas/leukemias (%)
		Liver (%)	Kidneys (%)	
DMBA→EMF	48	1 (2.1)	2 (4.2)	2 (4.2)
DMBA→Sham	48	0	2 (4.2)	2 (4.2)
DMBA→TPA	30	5 (16.7)	5 (16.7)	5 (16.7)
DMBA→Control	30	3 (10.0)	5 (16.7)	5 (16.7)

Table IV. Serum and plasma hormonal levels for melatonin, corticosterone and ACTH in mice treated with DMBA followed by EMF exposure or TPA treatment

Group	Serum hormonal level			Plasma hormonal level	
	No. of mice	Melatonin (pg/ml)	Corticosterone (ng/ml)	No. of mice	ACTH (pg/ml)
DMBA→EMF	5	3.5 ± 1.2	129.3 ± 54.2	6	259.2 ± 181.3
DMBA→Sham	5	3.3 ± 0.8	163.4 ± 39.2	5	197.0 ± 56.4
DMBA→TPA	5	<2.8	148.9 ± 43.6	5	264.2 ± 141.5
DMBA→Control	4	4.2 ± 1.6	209.8 ± 51.8	6	260.8 ± 143.3

[a]All five samples had values less than the detection limit (2.8 pg/ml).

transplacentally treated with ethylnitrosourea, is now under way in our laboratory.

In conclusion, 1.5 GHz EMF exposure did not promote DMBA-initiated mouse skin carcinogenesis under the present experimental conditions.

Acknowledgement

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