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# Microwave-Induced Post-Exposure Hyperthermia: Involvement of Endogenous Opioids and Serotonin

HENRY LAI, AKIRA HORITA, C. K. CHOU, MEMBER, IEEE, AND A. W. GUY, FELLOW, IEEE

*Abstract*—**Acute exposure to pulsed microwaves (2450 MHz, 1 mW/cm$^2$, SAR 0.6 W/kg, 2-$\mu$s pulses, 500 pulses/s) induces a transient post-exposure hyperthermia in the rat. The hyperthermia was attenuated by treatment with either the narcotic antagonist naltrexone or one of the serotonin antagonists cinanserin, cyproheptadine, or metergoline. It was not affected, however, by treatment with the peripheral serotonin antagonist xylamidine nor the dopamine antagonist haloperidol. It thus appears that both endogenous opioids and central serotonin are involved. It is proposed that pulsed microwaves activate endogenous opioid systems, and that they in turn activate a serotonergic mechanism that induces the rise in body temperature.**

## I. Introduction

IN PREVIOUS RESEARCH, we concluded that acute exposure to low-level, pulsed microwaves activates endogenous opioids in the rat on the basis of our findings that: 1) microwaves induced a post-exposure hyperthermia that was blockable by the narcotic antagonist naloxone [1]; 2) microwaves enhanced amphetamine-induced hyperthermia, an effect that was also blockable by naloxone [2]; 3) microwaves enhanced morphine-induced catalepsy [3]; and 4) microwaves attenuated the naloxone-induced withdrawal syndrome in morphine-dependent rats [1].

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The post-exposure hyperthermia was a most consistent response of rats to exposure to pulsed microwaves. In further experiments we found this effect to be classically conditionable to cues in the exposure environment and the conditioned response to be also attenuable by naloxone, suggesting the involvement of endogenous opioids [1], [2]. In this paper, we report further experiments elucidating the neural mechanisms underlying the post-exposure hyperthermia. They showed that serotonin in the central nervous system plays an important role in mediating the effect.

## II. Methods and Materials

### *Animals*

Male Sprague–Dawley rats (250–300 g), obtained from Tyler Lab., Bellevue, WA, were used. They were housed in a temperature-controlled vivarium (22°C) maintained at a 12-h light–dark cycle (lights on between 8 A.M. and 8 P.M.). They were housed four to a cage and provided with food and water *ad libitum*. Each animal was used once in the experiments.

### *Drugs and Controls for Drug Injection*

Drugs used consisted of the serotonin antagonists cinanserin (Squibb & Sons Inc., New Brunswick, NJ), cyproheptadine (Merck, Sharp & Dohme, West Point, PA), and metergoline (Soc. Pharmaceutici, Milano, Italy); a dopamine antagonist haloperidol (Haldol; McNeilab Inc.,

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Spring House, PA); a narcotic antagonist naltrexone hydrochloride (Endo Laboratories Inc., Garden City, NY); and a peripheral serotonin antagonist xylamidine tosylate (Wellcome Research Lab., Beckenham, Kent, England). Drugs were dissolved in distilled water immediately before injection. Naltrexone, haloperidol, and cinanserin were injected intraperitoneally at a volume of 1 ml/kg; cyproheptadine, metergoline, and xylamidine were injected at a volume of 2 ml/kg owing to their low solubility in water. Controls (for drug injection) received intraperitoneal injections of either 1 or 2 ml/kg of distilled water. There was no significant difference in responses between these two control groups, so the data were pooled and are reported together. Dosages reported in this paper are those of the bases of the drugs.

*Method of Microwave Irradiation*

Rats were irradiated with circularly polarized pulsed (2 $\mu$s, 500 pulses/s), 2450-MHz microwaves in waveguides developed by Guy *et al.* [4]. The spatially averaged power density in the waveguide was 1 mW/cm$^2$, and the average SAR was determined calorimetrically to be 0.6 W/kg for the size of animals used in these studies. (The power densities associated with a plane-wave irradiation of similar SAR would be approximately 3–6 mW/cm$^2$ [5].) Controls (for exposure procedure) were sham irradiated in similar waveguides simultaneously. The irradiation procedure was run blind, i.e., the experimenter doing the temperature measurements did not know which animals had received microwave or sham irradiation.

*Procedures of Drug Administration and Body Temperature Measurement*

Animals were irradiated in waveguides for 45 min. Their body temperature was then measured, and one of the following drugs or water (1 or 2 ml/kg) was injected intraperitoneally: cinanserin (10 mg/kg), cyproheptadine (1 mg/kg), haloperidol (0.5 mg/kg), metergoline (1 mg/kg), or naltrexone (1 mg/kg). Xylamidine injection (1 mg/kg, IP) was given 2 h before irradiation and the animals were injected with 1 ml/kg of water immediately after exposure. The first temperature measurement and drug/water injection were achieved within 1 min after exposure. Body temperature was then measured at 15-min intervals for 1 h. During this period, the animals were housed four to a cage in their home cages. Body temperature was monitored by a thermister probe (YSI-402, Yellow Springs Instrument) inserted 8 cm into the rectum and recorded by a YSI-43T thermometer (Yellow Springs Instrument). The thermister probe was inserted only during the time of body temperature measurement and removed afterwards. Experiments were run in an average ambient temperature of 22.0 °C (range: 21–24 °C).

*Data Analysis*

Temperature response curves during the 60-min post-exposure period were plotted as changes in body temperature from the time immediately after exposure (i.e., time zero) versus time. Response curves were analyzed by the nonparametric method of Krauth [6]. The curves were approximated by orthogonal polynomials, and the zero-order coefficients were compared by the 2-tailed Mann–Whitney U-test. Differences in temperature at 15 min postexposure among the various treatment groups were analyzed by the one-way analysis of variance, and differences between groups were determined by the Newman–Keuls Multiple-Range Test.

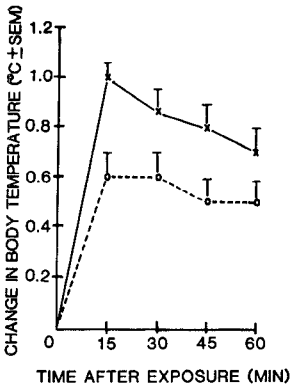


Fig. 1. Post-exposure changes in body temperature in rats injected with water immediately after exposure (time zero). X—microwave-exposed rats ($N=18$); 0—sham-exposed rats ($N=10$). Responses of microwave-exposed rats significantly higher than those of sham-exposed rats at $p < 0.02$ (Mann–Whitney U-test).

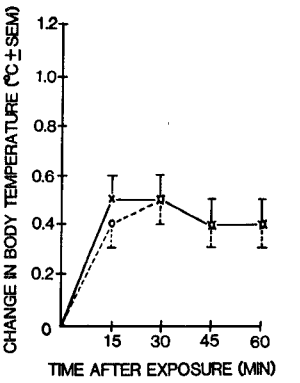


Fig. 2. Post-exposure changes in body temperature in rats injected with naltrexone (1 mg/kg, intraperitoneally (IP)) immediately after exposure. X—microwave-exposed rat ($N=15$); 0—sham-exposed rats ($N=9$).

## III. Results

After 45 min of exposure, microwaves did not significantly alter the body temperature. In animals pretreated with xylamidine, there was no significant difference in mean body temperature (°C ± SEM) immediately after exposure between the microwave- and sham-exposed animals (38.1 ± 0.1 ($N=6$) and 38.2 ± 0.1 ($N=10$), respectively). For the other animals in the study, mean body temperature (°C ± SEM) immediately after exposure for the microwave- and sham-exposed animals were 38.2 ± 0.1 ($N=74$) and 38.3 ± 0.1 ($N=52$), respectively.

Post-exposure changes in body temperature of the rats injected with water are shown in Fig. 1. The microwave-exposed rats had a significantly higher increase in body

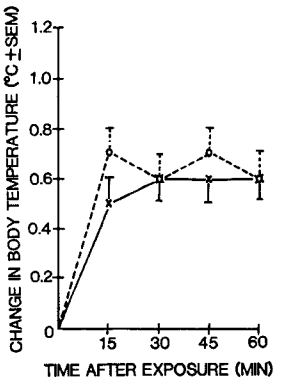


Fig. 3. Post-exposure changes in body temperature in rats injected with cinanserin (10 mg/kg, IP) immediately after exposure. X—microwave-exposed rats ($N = 15$); 0—sham-exposed rats ($N = 9$).

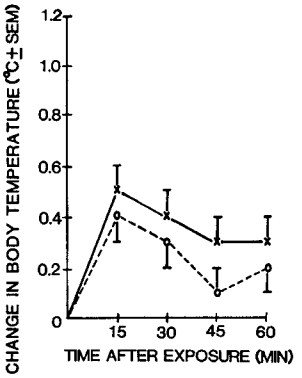


Fig. 4. Post-exposure changes in body temperature in rats injected with cyproheptadine (1 mg/kg, IP) immediately after exposure. X—microwave-exposed rats ($N = 15$); 0—sham-exposed rats ($N = 9$).

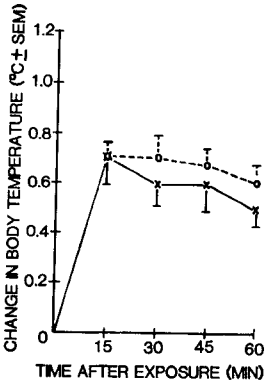


Fig. 5. Post-exposure changes in body temperature in rats injected with metergoline (1 mg/kg, IP) immediately after exposure. X—microwave-exposed rats ($N = 6$); 0—sham-exposed rats ($N = 10$).

temperature during the 60-min postexposure period than the sham-exposed animals ($p < 0.02$, Mann–Whitney U-test). Naltrexone treatment attenuated this effect of microwaves (Fig. 2) but did not affect the temperature response of the sham-exposed animals. The serotonin antagonists cinanserin (Fig. 3), cyproheptadine (Fig. 4), and metergoline (Fig. 5) also significantly attenuated the postexposure hyperthermia induced by microwaves. Cinanserin and metergoline did not significantly affect the responses of the sham-exposed rats. Cyproheptadine slightly, but not significantly, decreased the response ($p > 0.1$ sham + water versus sham + cyproheptadine). However,

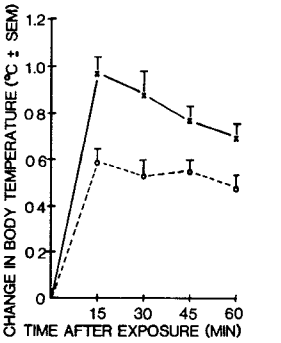


Fig. 6. Post-exposure changes in body temperature in rats pretreated with xylamidine (1 mg/kg, IP) 2 h before irradiation. The animals were also injected with 1 ml/kg of water intraperitoneally immediately after exposure. X—microwave-exposed rats ($N = 6$); 0—sham-exposed rats ($N = 10$). Responses of microwave-exposed rats significantly higher than those of sham-exposed rats at $p < 0.01$ (Mann–Whitney U-test).

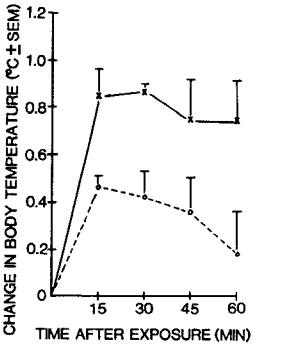


Fig. 7. Post-exposure changes in body temperature in rats injected with haloperidol (0.5 mg/kg, IP) immediately after exposure. X—microwave-exposed rats ($N = 5$); 0—sham-exposed rats ($N = 5$). Responses of microwave-exposed rats significantly higher than those of sham-exposed rats at $p < 0.02$ (Mann–Whitney U-test).

there was no significant difference in post-exposure temperature responses between the microwave- and sham-exposed rats treated with cyproheptadine. Furthermore, the postexposure hyperthermia induced by microwaves was not affected by treatment with xylamidine (Fig. 6) (responses of microwave-exposed rats significantly different from those of the sham-exposed rats at $p < 0.01$, Mann–Whitney U-test) nor haloperidol (Fig. 7) (responses of microwave- versus sham-exposed rats, $p < 0.02$, Mann–Whitney U-test).

Since the peak response of the post-exposure hyperthermia occurred at 15 min postexposure, changes in body temperature at 15 min postexposure of the different treatment groups were duly noted (presented in Table I) and statistical assessment of the treatment effects was made. One-way analysis of variance showed a significant effect from the different treatments ($F(13, 128) = 4.52$, $p < 0.01$). Pair-comparisons showed that naltrexone, cinanserin, cyproheptadine, and metergoline treatments significantly attenuated the effect of microwaves ($p$ at least smaller than 0.01 for each comparison). The effect was not significantly affected by haloperidol (responses of "MW + haloperidol" rats significantly higher than those of the "sham + haloperidol" rats at $p < 0.05$) nor xylamidine (responses of "MW + xylamidine" rats significantly higher than those of the "sham + xylamidine" rats at $p < 0.01$).

TABLE I
PEAK POST-EXPOSURE RESPONSES OF BODY TEMPERATURE IN DIFFERENT TREATMENT GROUPS

| Treatments | Change in body temperature at 15 min postexposure (°C ± SEM) |
|---|---|
| MW + water | 1.0 ± 0.06 (N = 18) |
| Sham + water | 0.6 ± 0.12 (N = 10)* |
| MW + naltrexone | 0.5 ± 0.08 (N = 15)* |
| Sham + naltrexone | 0.4 ± 0.09 (N = 9) |
| MW + cinanserin | 0.5 ± 0.10 (N = 15)* |
| Sham + cinanserin | 0.7 ± 0.13 (N = 9) |
| MW + cyproheptadine | 0.5 ± 0.09 (N = 15)* |
| Sham + cyproheptadine | 0.4 ± 0.08 (N = 9) |
| MW + metergoline | 0.6 ± 0.06 (N = 6)* |
| Sham + metergoline | 0.6 ± 0.10 (N = 10) |
| MW + xylamidine | 1.0 ± 0.07 (N = 6)** |
| Sham + xylamidine | 0.6 ± 0.06 (N = 10) |
| MW + haloperidol | 0.8 ± 0.10 (N = 5)*** |
| Sham + haloperidol | 0.5 ± 0.05 (N = 5) |

One-way analysis of variance of treatment groups, $F(13,128) = 4.52$, $p < 0.01$.

Newman–Kauls Multiple-Range test: *Different from "MW + water" group at $p < 0.01$; **Different from "sham + xylamidine" group at $p < 0.01$; ***Different from "sham + haloperidol" group at $p < 0.05$.

## IV. CONCLUSIONS

In previous research, we showed that acute exposure to pulsed microwaves elicits a post-exposure hyperthermia that is blocked by the narcotic antagonist naloxone (1 mg/kg, SC). In the present experiments, we found that the hyperthermia is also blockable by a second narcotic antagonist, naltrexone. These findings give further support [7] to our hypothesis that the post-exposure hyperthermia is mediated by endogenous opioids activated by the pulsed microwaves. It may be significant to point out here that (in the experiments reported previously) a more pronounced increase in body temperature was seen in sham-irradiated animals injected with water *subcutaneously* than in this experiment in sham-irradiated animals injected with water *intraperitoneally* [1]. Apparently, subcutaneous injection of water is more stressful than intraperitoneal injection. Stress has been shown to activate endogenous opioids, and this, in turn, induce hyperthermia [8]. Thus, the hyperthermia seen in the sham-irradiated rats injected subcutaneously with water could be partially attenuated by naloxone. After naloxone treatment, the response of the sham-irradiated rat injected subcutaneously with water is similar to that of the sham-irradiated rat injected intraperitoneally with water. The remaining hyperthermia has an unknown mechanism and has been shown to be unaffected by narcotic antagonists, and is thus unrelated to endogenous opioids.

In the present experiment, we found the post-exposure hyperthermia to be blockable by treatments with the putative serotonin antagonists cinanserin, cyproheptadine, and metergoline [9]. These drugs have different "side effects" on other transmitter systems, e.g., the cholinergic system, but their common property is antagonism of serotonergic functions in the brain. These data strongly suggest the involvement of a serotonergic mechanism in the post-exposure hyperthermia. Furthermore, the fact that the hyperthermia was not affected by treatment with the peripheral serotonin antagonist xylamidine [10], [11] implies that the serotonergic mechanism activated by microwaves is located in the central nervous system. Since naltrexone and serotonin antagonists attenuate the hyperthermia to the same extent, the implication is that they block different steps of the same neural mechanism.

Serotonin in the brain has been known to be involved in the regulation of body temperature [12]. Indeed, it was reported in a recent paper that mice with impaired thermoregulatory functions due to serotonin injection showed an increase in body temperature when exposed to an otherwise "nonthermal" dose of microwaves [13]. This result suggests that a serotonergic mechanism may be involved in thermoregulation in normal animals during exposure to low-level microwaves. A serotonergic-hyperthermia mechanism has been reported in the rat recently [14]. Like the post-exposure hyperthermia induced by microwaves, hyperthermia induced by activation of this serotonergic mechanism has been shown to be attenuated by cinanserin, cyproheptadine, and metergoline and also by treatment with the serotonin depletor para-chlorophenylalanine. This system has also been shown to be unaffected by the dopamine antagonist haloperidol. Recently, we have found this mechanism to be related to endogenous opioids (unpublished results).

Indeed, serotonin has been shown in many instances to play a role in mediating the effects of endogenous opioids. Martin and Bacino [15] have shown the hyperthermia induced by injection of $\beta$-endorphin into the preoptic anterior hypothalamus to be blockable by cyproheptadine; it thus appears that serotonin mediates $\beta$-endorphin-induced hyperthermia in the rat. $\beta$-endorphin enhances the metabolism of serotonin in the brain [16]; the hypotensive effect has been reported to be blocked by a serotonin antagonist and potentiated by the serotonin reuptake blocker fluoxetine [17]. Furthermore, the analgesic effect of $\beta$-endorphin was potentiated, whereas the development of tolerance after its repeated administration could be blocked by treatment with the serotonin-synthesis precursor 5-hydroxytryptophan; thus, a role is played by serotonin in these effects [18]. These data suggest a serotonergic synapse downstream from the endogenous opioid neurons. We therefore propose the following model for the neural mechanism of postexposure hyperthermia (Fig. 8). Pulsed microwaves activate endogenous opioids, probably $\beta$-endorphin, which, in turn, activate a hyperthermia-inducing serotonergic mechanism. The endogenous opioid system can be blocked by the narcotic antagonists naloxone and naltrexone, whereas the serotonergic mechanism is sensitive to serotonergic antagonists. This system is probably located in the preoptic anterior hypothalamic area of the rat brain.

It would be interesting to investigate whether microwave exposure would affect other serotonin-related functions in animals, e.g., sleep, learning, regulation of hormone secretion, autonomic functions, responses to stress, and motor functions [19], [20]. In humans, a cluster of syndromes (serotonin–irritation syndromes), including anxiety, flushing, headache, and hyperperistalsis, have been described in

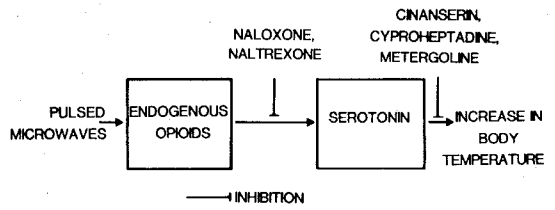


Fig. 8. A schematic model of the neural pathway of microwave-induced post-exposure hyperthermia. Pulsed microwaves activate endogenous opioids, which in turn activate a serotonergic mechanism that produces hyperthermia. Activity of the endogenous opioid system is blockable by the narcotic antagonists naloxone and naltrexone; whereas that of the serotonergic mechanism is blockable by the serotonin antagonists cinanserin, cyproheptadine, and metergoline.

hyperserotonergic states, such as in migraine [21] and exposure to high-voltage electrical devices [22]. It would be interesting to determine whether high levels of, or chronic exposure to, microwaves would produce these syndromes.

## ACKNOWLEDGMENT

The authors thank A. Dong and E. Carino for technical assistance.

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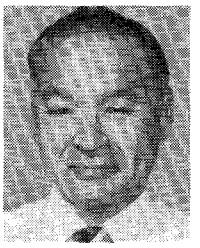

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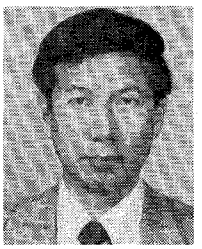

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During his graduate study at the University of Washington, he had extensive training in both electromagnetics and physiology. He spent a year as an NIH Post-Doctoral Fellow in the Regional Primate Research Center and the Department of Physiology and Biophysics at the University of Washington, and became an Assistant Professor in the University's Department of Rehabilitation Medicine, in 1977. Currently, he is a Research Associate Professor in the Center for Bioengineering and Department of Rehabilitation Medicine, as well as Associate Director of the Bioelectromagnetics Research Laboratory. He is engaged in teaching and research in electromagnetic dosimetry, exposure systems, biological effects of microwave exposure, and RF hyperthermia for cancer treatment. He is a consultant for the NCRP's Scientific Committee 53 on the biological effects and exposure criteria for radio frequency electromagnetic fields, and he has also served on the ANSI Subcommittee C95.4 since 1978, and is now the chairman of 3-kHz–3-MHz working group.

Dr. Chou was the chapter chairman of IEEE's Seattle Section on Antennas and Propagation/Microwave Theory and Technique in 1981–1982. He is now on the Board of Directors of the Bioelectromagnetics Society. In 1981, he received the first special award for the decade of the 70's for contributions in medical and biological research from the International Microwave Power Institute. He is a member of BEMS, AAAS, IMPI, the Radiation Research Society, Tau Beta Pi, and Sigma Xi.

**Arthur W. Guy** (S'54–M'57–SM'74–F'77) was born in Helena, MT, on December 10, 1928. He received the B.S. degree in 1955, the M.S. degree in 1957, and the Ph.D. degree in 1966, all in electrical engineering from the University of Washington, Seattle.

From 1947 to 1950 and from 1951 and 1952, he served in the U.S. Air Force as an Electronic's Technician. Between 1957 and 1964 he was a Research Engineer in the Antenna Research Group, Boeing Aerospace Co., Seattle, WA. While there, his field included research on broad-band and microwave devices, surface wave antennas, propagation through anisotropic dielectrics, and antennas buried in lossy media. Between 1964 and 1966 he was employed by the Department of Electrical Engineering, University of Washington, conducting research on VLF antennas buried in polar ice caps. At that time, he also served as Consultant to the Department of Rehabilitation Medicine, working on problems associated with the effect of electromagnetic fields on living tissue. In 1966, he joined the faculty of the Department of Rehabilitation Medicine. Presently, he is a Professor in the Center for Bioengineering, has a joint appointment as Professor in Rehabilitation Medicine and adjunct Professor in Electrical Engineering. He is involved in teaching and research in the area of biological effects and medical applications of electromagnetic energy.

Dr. Guy is a member of COMAR, ANSI C-95 Committee, and Chairman of the 1970–1982 Subcommittee IV that developed the protection guides for human exposures to radiofrequency fields in 1974 and 1982, NCRP, and chairman of Scientific Committee 53 responsible for biological effects and exposure criteria for radiofrequency fields, Armed Forces National Research Council Committee on Vision Working Group 35, Commission A Radio Measurement Methods and URSI, ERMAC, and the EPA Scientific Advisory Board Subcommittee on Biological Effects of Radiofrequency Fields. He also serves as a consultant to the NIEHS on the USSR–U.S. Environmental Health Cooperative Program and was a member of the NIH Diagnostic Radiology Study Section 1979–1983. He is a member of the editorial boards of the *Journal of Microwave Power* and IEEE TRANSACTIONS ON MICROWAVE THEORY AND TECHNIQUES.

Dr. Guy holds memberships in Phi Beta Kappa, Tau Beta Pi, and Sigma XI. He is also a member of the American Association for the Advancement of Science, and is current President of the Bioelectromagnetics Society.

# Short Papers

## Focused Electromagnetic Heating of Muscle Tissue

POVL RASKMARK AND J. BACH ANDERSEN

*Abstract*—**A cylinder of muscle tissue may be heated at depth by applying an electric field to a circumferential gap in a metallic cylinder surrounding the tissue. Experiments at 150 MHz on a 10-cm-diameter cylinder verify the theoretical calculations and show a well-defined focus on the axis.**

### I. INTRODUCTION

In cancer treatment, the use of elevated temperatures in tumors (hyperthermia) has now been established as a very promising supplement to other therapies. For the proper selective treatment of the tumor cells, it is important that the healthy tissue not be overheated, so technical means for creating a hot spot or focus in the tissue are of interest. There is especially a need for heating deep-seated tumors, since superficial ones may be treated by a variety of techniques. In muscle tissue or other "wet" tissues, focusing at depth is made difficult by the fact that the attenuation in the medium is large; penetration depths and wavelengths are comparable. Focused heating has been considered at microwave frequencies [1], [2], but here the concern is with lower frequencies, around 100 MHz, in order to explore the potentialities of deep penetration. Previously [3], it has been shown theoretically in a two-dimensional case that a symmetric distribution of sources around the axis of cylinder may create a maximum of power at the center. This short paper reports on experimental and theoretical results for an especially simple applicator around a cylindrical structure.

### II. A COAXIAL APPLICATOR

The applicator shown in Fig. 1 is applied to a cylindrical shape of tissue, or tissue supplemented with water to form the shape of a cylinder. The lossy medium is surrounded by a shell of low-loss dielectric of thickness $d = (b - a)$, and this again is surrounded by a metal cylinder with a circumferential gap of width $w$. Thus, a gap-excited coax transmission line with the tissue as the center conductor is provided. This configuration has been analyzed numerically by assuming a field distribution in the gap between the two metal edges and the following conclusion may be drawn from the simulation: power distribution is sensitive to the frequency, gap width $w$, and insulator spacing $d$.

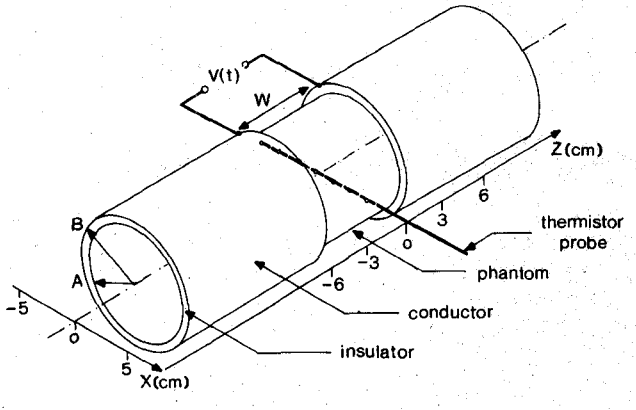


Fig. 1. Cylindrical applicator and phantom. The RF voltage is distributed around the gap. The thermistor probe is shown in the gap center ($z = 0$). Difference in radius $A$ and $B$ correspond to insulator thickness.

First, the frequency is chosen such that the radius of the lossy medium approximately equals the focal spot size in a lossy medium [6], $\rho_M$, where

$$(k_0\rho_M)^2 = \frac{8\epsilon^1}{3(\epsilon^1)^2 + (\epsilon^{11})^2}.$$

This choice of frequency may lead to a local maximum of power on the axis of the cylinder if reactive nearfields are sufficiently small. In simple words, the frequency is chosen so low that the exponential decay into the tissue is avoided, and so high that

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