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EVALUATION OF DRUGS FOR PREVENTION OF HYPERTHERMIA IN RATS EXPOSED TO MICROWAVE IRRADIATION

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The objective of this study was to determine the effectiveness of two antipyretic drugs, indomethacin and dihydrotachysterol, in the prevention of microwave-induced hyperthermia in rats. Indomethacin has been proven effective in reducing fever of pyrogenic origin. Dihydrotachysterol (DHT) is effective in increasing survival of rats during heat stress.

Female Long-Evans rats, 250-300 g, were equally divided into two experimental groups -- an AM group and a PM group. Each group served as both drug-treated and nontreated controls during the course of the study. After being acclimated to restraint in an acrylic cone-shaped holder and to the presence of a colonic temperature probe, each rat was subjected to a series of body temperature measurements under various drug and microwave conditions. Before microwave irradiation, time was allowed for each rat's colonic temperature to reach equilibrium (2 h in the AM group, 1 h in the PM group). Microwave irradiation (1.28 GHz,

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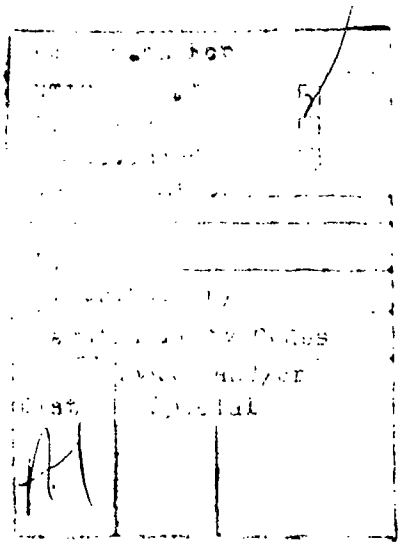
370 pps, 3 μs pulse duration) was administered at a power density intensity of 43 mW/cm^2 resulting in a calculated average specific absorption rate (SAR) of 8.6 W/kg.

Pretreatment with both drugs consisted of single and multiple injections prior to microwave exposure. Multiple doses of DHT caused a progressive fall in baseline body temperature, but did not affect the relative increase in temperatures due to microwave irradiation. Single injection procedures did not reduce temperature elevation due to microwave irradiation. Neither indomethacin nor DHT were found to ameliorate microwave-induced hyperthermia.



SUMMARY PAGE

THE PROBLEM

Hyperthermia as a consequence of exposure to microwave irradiation is a concern of safety personnel. Ideally, military operations should be provided with personnel free of pathological responses to electromagnetic radiation. As yet, a prophylactic treatment for microwave-induced fever is unknown. We studied the effectiveness of two antipyretic drugs, indomethacin and dihydrotachysterol, for the prevention of microwave-induced hyperthermia in rats. Indomethacin reduces fever of pyrogenic origin, and dihydrotachysterol (DHT) increases survival of rats during heat stress.

FINDINGS

Pretreatment with both drugs consisted of single and multiple injections prior to microwave exposure. Multiple doses of DHT caused a progressive fall in baseline body temperature but did not affect the relative increase in temperatures due to microwave irradiation. Single-injection procedures did not alter microwave-induced increases in body temperature. Neither indomethacin nor DHT were found to ameliorate microwave-induced hyperthermia.

RECOMMENDATIONS

Further study should focus upon drug-induced changes that readily promote beneficial thermoregulation and, in particular, heat dissipation from the body. One such drug is DHA (dehydroepiandrosterone), which has been shown effective in preventing deaths of rats exposed to 37 °C ambient temperature. Another direction of investigation should be the use of a unique strain of rat that does not manifest fever as do normal rats when exposed to bacterial endotoxin. This strain is deficient in antidiuretic hormone (ADH) and consequently has diabetes insipidus (DI). A DI-rat, also known as Brattleboro rat, has both unusually high water intake and rate of urination. Consideration might be given to antipyretics that cause hypothermia at thermoneutral ambient temperatures.

ACKNOWLEDGMENTS

We thank Mr. Clayton Ezell for designing and fabricating the Plexiglas rat holders, and the personnel of the NAMRL Veterinary Sciences Department for their excellent care of the rats. We are deeply grateful to Dr. John de Lorge for his encouragement and advice during this pilot study. Thanks are due Mrs. Anna Johnson and Mr. Delbert Turner, deceased, for preparing the manuscript in its final form, and also to Mr. R. E. Barrett and Mr. C. P. Morgensen for their art work. We are indebted to Dr. A. G. Rogers, Jr., R.P. Scherer, North American, and Dr. C. A. Stone, Merck Sharpe & Dohme, for their kind support by providing drugs. Reviews and comments by our colleagues, Drs. M. Ballinger, J. D'Andrea, T. D. David, J. Lords, and G. Lotz, are also greatly appreciated.

The animals used in this study were handled in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals, prepared by the Committee on Care and Uses of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council, DHHS, NIH Publication No. 85-23, 1985, and The Animal Welfare Act of 1966, as amended.

INTRODUCTION

Increased body temperature in animals exposed to microwaves has been well documented and summarized in recent reviews (2,10,14). In contrast, pharmacological prevention and treatment of microwave-induced hyperthermia has not been thoroughly investigated. Consequently, we initiated a series of rat studies to determine the feasibility of using drugs to prevent hyperthermia. The two drugs that were selected, indomethacin and dihydrotachysterol (DHT), have antipyretic and hypercalcemic properties, respectively.

Krupp and Ziel (13) stated that evidence supports the hypothesis that the antihyperthermic action of antipyretic drugs depends on their ability to inhibit the synthesis of prostaglandins, especially since the treatment of febrile reactions with antipyretics reduces both body temperature and prostaglandin concentration in cerebrospinal fluid. We chose indomethacin for this pilot drug study because of its effectiveness as a potent single-dose antipyretic compound in rats (3,9,20).

Several investigators have studied various aspects of the effect of dry heat on rats. They have shown that marked heat stress in rats occurs at ambient temperatures exceeding 34 ^{o}C (6), but death can be prevented at ambient temperatures exceeding 36 ^{o}C by daily treatment with a hypercalcemic drug, DHT (15,17). Therefore, DHT was evaluated here in single and multiple doses in the prophylactic treatment of microwave heat stress in rats.

MATERIALS AND METHODS

The study was initiated with 13, female, Long-Evans rats (Charles River Breeding Laboratories), 45 days old. They were housed in individual rack-mounted wire cages in a room maintained at 21-25 ^{o}C with continuous light during the study. The rats were given water and commercial rodent chow ad libitum except during study procedures.

The microwave-exposure system consisted of an anechoic chamber (3.4 x 2.20 x 2.35 m high) shielded with copper and lined with 0.204-m pyramidal absorber (AAP-8, Advanced Absorber Products), as previously described (11). A Styrofoam wall was placed anterior to the absorber near the wall opposite the radiation source (a horn) to permit better ambient temperature control. The exposure chamber was equipped with a closed-circuit television camera, lights, and speakers. General illumination was provided by a white 60-W light above the horn. With the radar set and the ventilation fans and white noise in operation, the sound pressure level was 79 dB. Air in the exposure chamber was circulated by fans at a rate exceeding 28 m^3/min. The ambient temperature was measured 0.3 m above the animal and ranged between 23 and 27 ^{o}C. Humidity was measured at the start and end of each session with an EL-TRONICS Model 106 hygrometer (Warren Components Division, EL-TRONICS Incorporated). The average humidity was 60% throughout the day.

The microwave field was generated by a radar set (AN/TPS-G, Hazeltine Corporation), which provided a pulsed-wave source operating at 1.28-GHz microwaves, pulsed at 370 pps and a pulse duration of 3 μs. A custom-made horn was connected with a coaxial transmission line to the radar. Rats were irradiated individually in flat-bottomed, tapered cylindrical, acrylic, rodent restrainers (Fig. 1). The rat holder was positioned such that the long axis of the rat was parallel to the H-field with the rat's left lateral surface exposed to the radiation source.

Power density measurements were made with a Narda microline isotropic probe (Model 8323, Narda Microwave Corporation) at 1.35 m from the radar horn. The power density was 43 mW/cm^2. Based on tables in Durney et al. (8), average specific absorption rate (SAR) was 8.6 W/kg. The formula $2D^2/\lambda$, where D = diagonal of the horn opening and λ = irradiation wave length, was used to define the minimum far field.

Animal colonic temperature 6 cm beyond the anal sphincter was measured either with a Vitek Model 101 electrothermia monitor (Vitek) or a Luxtron Model 1000B biomedical Fluoroptic™ thermometer (Luxtron). Pre-experiment calibrations of the instruments assured identical temperature readings. The temperature monitor was located outside and near the microwave exposure chamber.

ADAPTATION TO RESTRAINT

At 79 days of age and continuing through 103 days of age, 12 rats were gradually adapted to the restraint device. Thirteen such daily sessions were conducted, which resulted in 2 groups of rats that were habituated either to at least 4 h (n = 6, AM group) or 3.5 h (n = 6, PM group) of restraint.

COLONIC TEMPERATURE MEASUREMENTS

When rats were 108 to 197 days old, they were conditioned to being routinely restrained and to having a soft, flexible polyethylene tube (2 mm outside diameter) inserted at least 6 cm past the anal orifice. The tube remained in situ for the entire restraint session. The colonic catheter was taped to the base of the tail. One end of the 0.25-m long tube was sealed by low temperature heat and then manipulated into a smooth, round tip that could be easily passed through the anus and into the large intestine. This catheter served as a conduit for the temperature probe used to measure colonic temperature. During each of 32 sessions of colonic-catheter conditioning, colonic temperature measurements were taken at 30-min intervals.

Figure 1

Rats restrained in Plexiglas holders on laboratory table adjacent to microwave exposure chamber. Note the colonic catheters near the tail areas.

DRUG ADMINISTRATION AND MICROWAVE EXPOSURE

Once a week from day 208 through 302 days of age and immediately after being given a drug dose, each rat was positioned inside the microwave irradiation chamber. Successive weekly treatments were:

week 1: no drug, no microwave irradiation (MW)
week 2: no drug, MW
week 3: 2-ml isotonic saline (i.p.), MW
week 4: indomethacin (i.p.), MW
week 5: DHT (i.p.), MW.

Then, a week later, a multiple-dose DHT series was initiated. Rats were injected once a day for either 4 or 5 days:

week 1: no drug, MW
week 2: 5 DHT injections (i.p.), MW once
week 3: 4 DHT injections (i.p.), MW once
week 4: 5 DHT injections (i.p.), MW once
week 5: 5 DHT injections (i.p.), MW once.

Colonic and ambient temperature were measured every 15 min. The AM group rats ($\underline{n}$ = 5) were equilibrated for 2 h before being irradiated for 1 h; PM group rats ($\underline{n}$ = 5) were equilibrated during the first hour and then irradiated for 1 h. The rats remained undisturbed for 30 min following irradiation. The radiation session was terminated if a rat's colonic temperature reached 41.5 ^{o}C, the point at which Adolph (1) reported fatalities.

PHARMACEUTICALS

Indomethacin, in 25-mg capsules (Merck, Sharp & Dohme), was dissolved in isotonic sodium chloride so that a 2-ml injection (i.p.) contained indomethacin at 3.33, 6.67, 8.33, or 10 mg/kg BW. The contents of capsules containing 0.125 mg of crystalline DHT in sesame oil (Withrop Laboratories) were used for DHT injections. The contents were aspirated and immediately injected (i.p.) into the rat at doeses of DHT approximately 0.416 mg/kg BW.

Student's t-statistic (two-tailed test) was used to determine the probability associated with difference between means (P). All P values of 0.01 or less were considered significant.

RESULTS

Figure 2 shows a comparison of the temperatures of AM and PM groups during restraint on a laboratory table on the last 5 days prior to starting the microwave exposures. At the beginning of each session, colonic temperatures were about the same. In time, however, temperatures of the two groups became significantly different with PM group means at least 0.5 ^{o}C higher than the AM group means. If asymptotes for the two curves in Figure 2 are projected, the AM group seems to have reached colonic

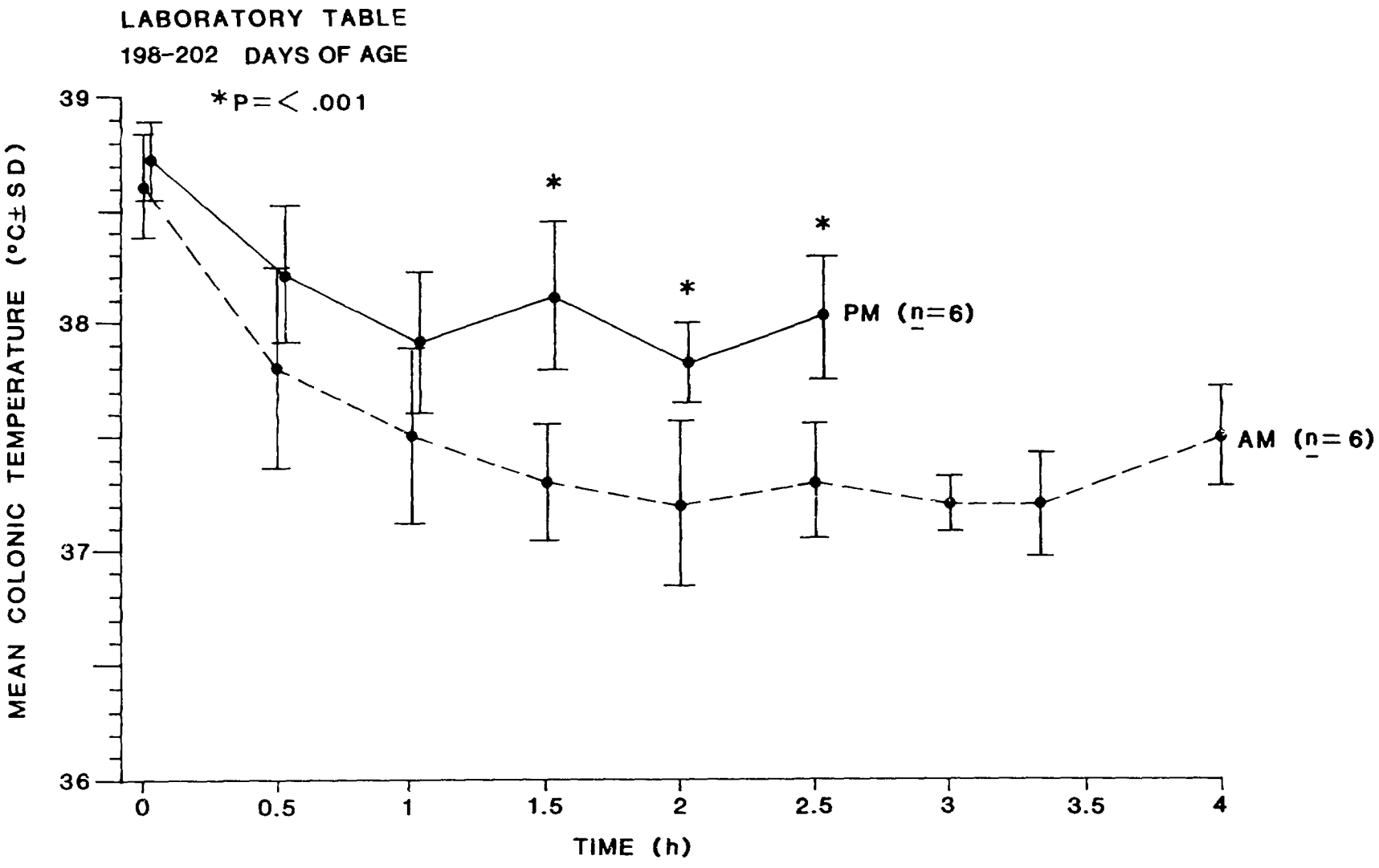


Figure 2

Mean colonic temperature of AM group and PM group rats (250-300 g) restrained on a laboratory table. Each mean value represents five successive daily measures of six rats.

temperature equilibrium after about 2 h of restraint and the PM group after about 1.5 h.

Figure 3 illustrates the similarity of mean colonic temperature response of the rats to microwave exposure regardless of the kind of pre-exposure treatment. Both indomethacin and DHT failed to prevent microwave-induced hyperthermia. Note in this figure, the PM group, which was irradiated after 1 h of restraint, had a higher mean colonic temperature at microwave onset (∿38 vice ∿37 °C) and less increase during irradiation (∿+3 °C vice ∿+ 3.5 °C). Because of high body temperature, exposure of a PM-group rat (indomethacin treated) was terminated, which accounts for the lowered point of that curve at 2 h.

The results of administering DHT in multiple preventive doses to the AM-group rats, following the single dose series, are given in Figure 4. Multiple doses did not prevent hyperthermia caused by microwave irradiation. Although the degree of hyperthermia did not change, a pre-exposure hypothermia became more pronounced with successive DHT injections. The PM group reacted similarly, except that the mean colonic temperature at the start of microwave exposure was higher. Consequently, irradiation of the PM group frequently did not continue for a full hour because of high body temperature (41.5 °C). The AM group's pre-exposure mean colonic temperature during the fifth week (after a total of 10 DHT doses) was lower than the PM group's (35.4 vice 37.2 °C). Therefore, DHT caused more pronounced hypothermia among the AM group rats.

Repeated injections of DHT caused about a 28% mean drop in body weight during the 4-week dosing period and resulted in the deaths of 3 animals. An additional two animals died the week following DHT treatment.

During the course of the experiment, mean animal weights increased from 220 to 330 g.

DISCUSSION

It has been shown in animals (5,13) that the antihyperthermic action of antipyretic preparations depends on their ability to inhibit synthesis of exogenous-pyrogen affected prostaglandins. The treatment of hyperthermia with antipyretics reduces not only body temperature but also the concentration of prostaglandin in the cerebrospinal fluid. Because we obtained similar hyperthermic responses following several kinds of pre-exposure preparations (no injection, isotonic saline, indomethacin, DHT), we infer that the microwave exposure did not influence production of antipyretic-susceptible prostaglandins. The antipyretic we selected, indomethacin, was found to be the most potent of several antipyretics tested by different laboratories (9,10,13). We cannot eliminate the possibility of a specific pharmacologic-susceptible prostaglandin being produced by microwave irradiation.

Brodie and Kundrats (3) exposed rats to radiant heat from an infrared lamp at different heights above a mesh cage and found that indomethacin, 4 mg/kg BW (i.p.), did not alter infrared-induced hyperthermia. Our

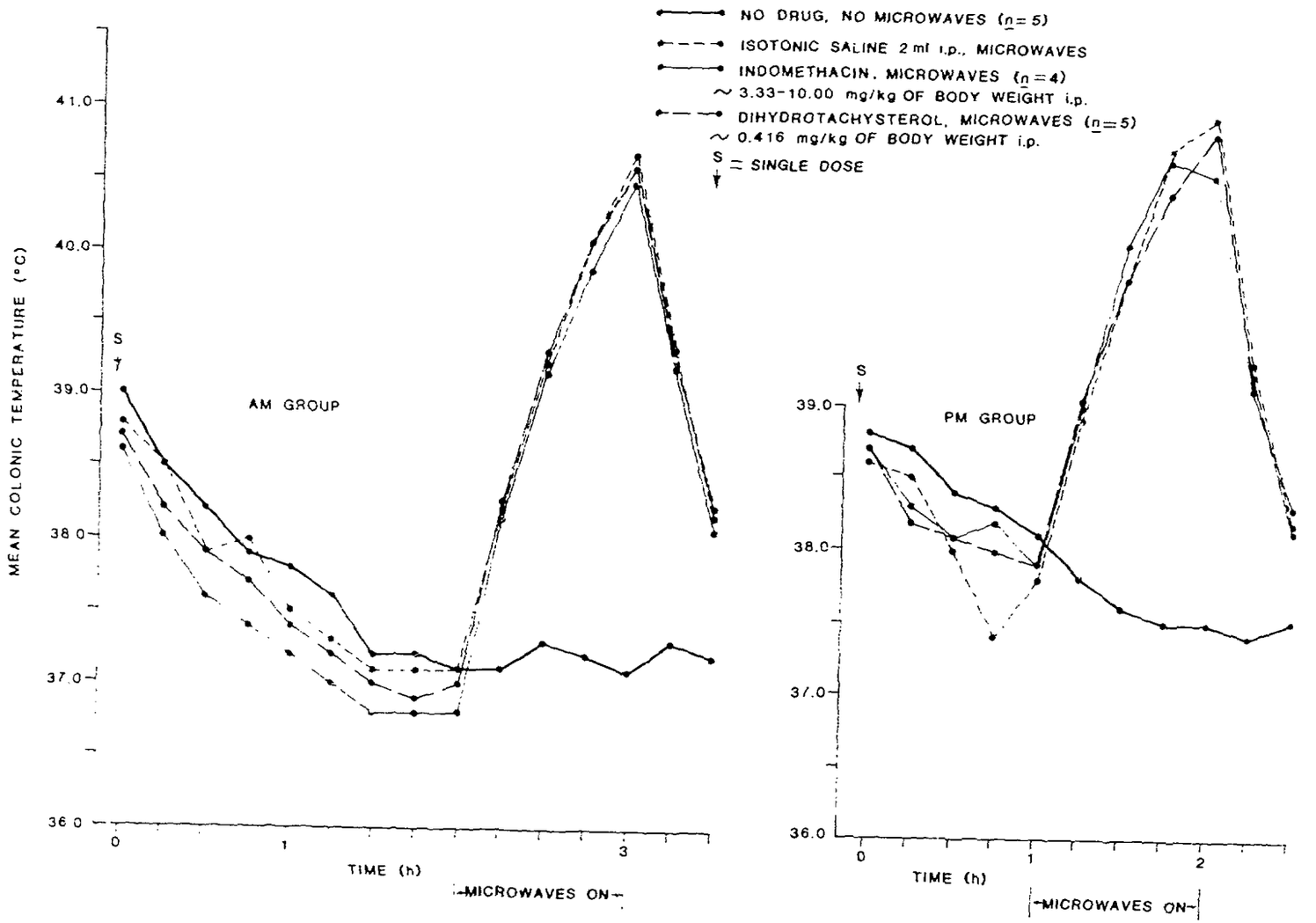


Figure 3

Series of mean colonic temperatures for AM group rats (273 ± 24 g, n = 5) and PM group rats (277 ± 23 g, n = 5) taken when restrained inside a microwave chamber after having either sham injection or an intraperitoneal (i.p.) injection of a given substance.

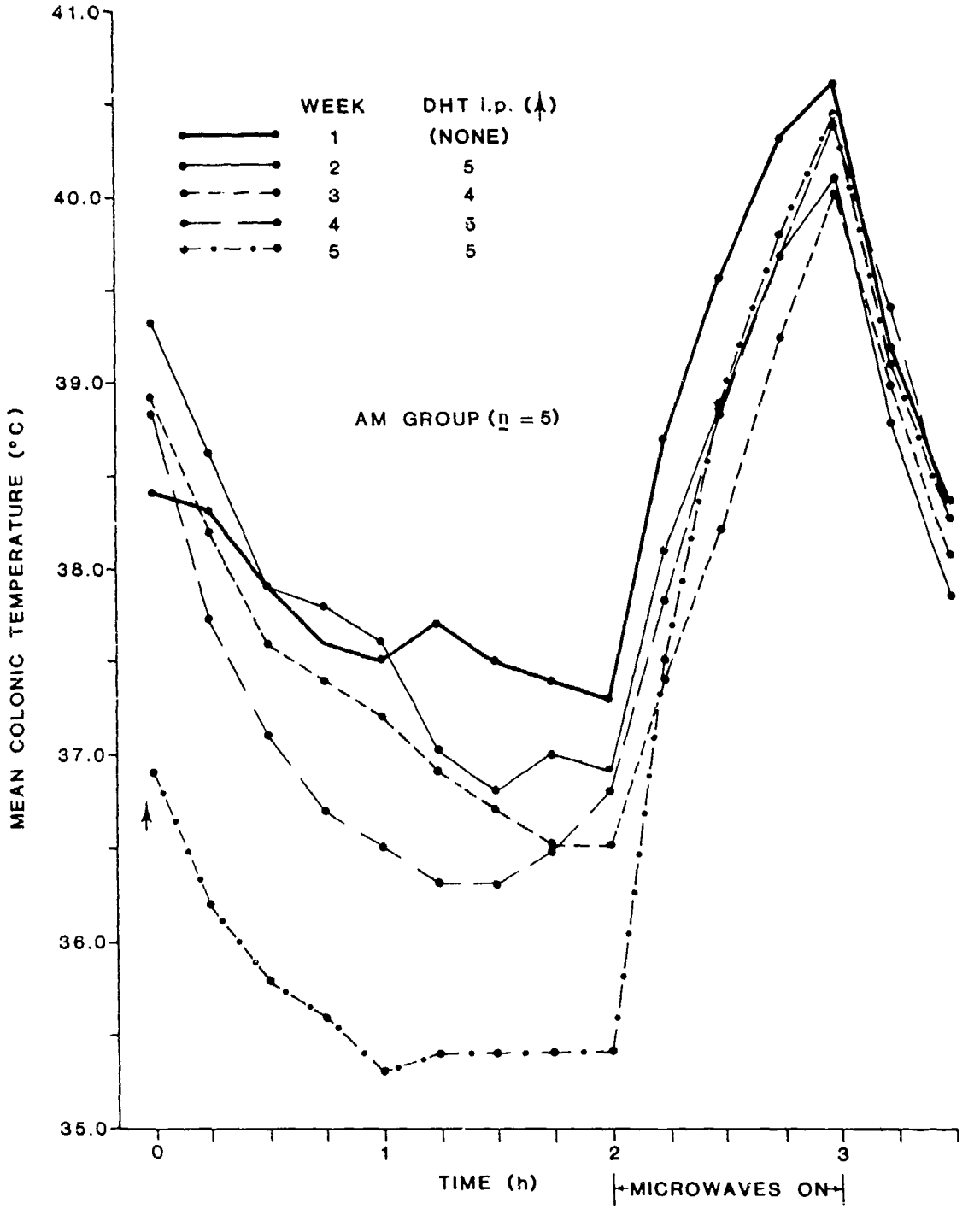


Figure 4

A series of mean colonic temperatures taken from AM group rats (273 ± 24 g, n = 5) restrained and exposed to microwaves. They were given 19 intraperitoneal injections of crystalline dihydrotachysterol (DHT) over a 4-week period. Each dose contained approximately 0.416 mg DHT per kg of body weight.

indomethacin results were also negative with a microwave source for heating and larger doses up to 10 mg/kg BW (i.p.). Future drug assays for treatment of microwave-induced hyperthermia might include antipyretics that cause hypothermia at thermoneutral ambient temperatures.

An estimation of the probable cause of PM-group member aborts during irradiation can be obtained by comparing their curves in Figure 3 with the corresponding AM group curves. Notice that the PM group's "microwave-on" temperatures were about 1 ^{o}C higher than those of the AM group; that at "microwaves-off" the PM group's mean temperature was about 0.5 ^{o}C higher than that of the AM group, and there was a single abort of one of the PM group rats. Essentially, 43 mW/cm^{2} power density microwaves for 1 h consistently caused an increment greater than 3 ^{o}C, and thus, the absolute "microwaves-on" colonic temperature value influenced the final absolute "microwaves-off" value. This would explain the reason for no aborts during the AM group sessions (relatively low absolute "microwaves-on" colonic temperatures) and for the aborts within the PM group (relatively high absolute "microwaves-on" colonic temperatures). Note also in Figure 3 that the corresponding starting and ending mean colonic temperatures of both groups are about the same in every respect and that the ascending and descending temperature slopes are similar.

Animals receiving single doses of either indomethacin or DHT revealed no toxic signs. However, after the single-dose experimental series, the same rats given multiple DHT doses developed signs of DHT toxicity: drastic loss of body weight, nose bleeding, shedding of hair, dull coat, poor ambulation, anorexia, and death of five animals. These signs of DHT toxicity have been described by Chen et al. (4) and Djojosoebagio and Turner (7).

To what other groups of pharmacologicals may we go for specific drugs that would possibly prevent microwave-induced hyperthermia? Considering that there are several kinds of quantum bio-effects of microwave energy (2, 10), the most reasonable possibilities of effective prevention and treatment may be those drugs that readily promote beneficial thermoregulation and, in particular, heat dissipation from an animal's body. Such drugs in single or multiple doses, alone or in various combinations, may enhance mammalian heat dispersing and regulatory abilities by acting on various bodily functions. Some of the effective adjustments brought by antihyperthermic administration might be: simultaneous systemic vasoconstriction and peripheral vasodilation, reduction of metabolic rate, increased sweating, lowering of set-point in the hypothalamus, adequate maintenance of equilibrium between heat production and heat loss, and blockage of response to cold (sympathoadrenal responses).

There are many experimental approaches to control hyperthermia. One approach, based on the work of Tal and Sulman (16), demonstrated that a weak androgen, dehydroepiandrosterone (DHA), was effective in preventing deaths of rats exposed to 37 ^{o}C ambient temperature. They suggested that DHA blocks hypothalamic thermoreceptors and, consequently, reactivates the negative-feedback thyrotropin-thyroxin mechanisms.

Another approach uses the Brattleboro rat (18), which is a Long-Evans strain mutant that is deficient in antidiuretic hormone (ADH) and has diabetes insipidus (DI). The latter condition causes unusually high water intake and urine elimination. Commonly referred to as the DI rat, it does not develop fever, as do normal rats, following an intracerebroventricular injection of bacterial endotoxin. However, Veale et al. report (19) that if DI rats are given subcutaneous injections of ADH, they will develop fever of bacterial endotoxin origin. They proposed that ADH is necessary for adequate production of endogenous pyrogen, which initiates the fever response to bacterial endotoxin. More recent findings by Kovacs and De Wied (12) revealed that bacterial endotoxin-induced fever was suppressed in normal rats by ADH. Is the thermoregulatory system of the DI rat adequate for coping with microwave irradiation? What is the role of ADH during hyperthermia? Answers to both of these heuristic questions may be profitable.

SUMMARY

Restrained, female, Long-Evans rats given pre-exposure intraperitoneal doses of indomethacin, antipyretic drug, and crystalline dihydrotachysterol (DHT), a hypercalcemic, had a uniform hyperthermic response during 1-h exposures (mean colonic temperature increase > 3 ^{o}C) to microwaves (1.28 GHz, 370 pps, 3 us duration). A similar temperature response to microwave irradiation occurred following either sham injection or isotonic saline. Power density with the rat H-polarized was 43 mW/cm^{2}, which produced an average specific absorption rate of 8.6 W/kg, as determined from handbook information (8). The pharmacologically active substances did not prevent microwave-induced elevations of body temperature. Repeated DHT doses (19 during a 28-day period) resulted in drastic hypothermia evident at the end of the pre-exposure equilibration period, but did not alter the microwave response, either.

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