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# Microwave Facilitation of Domperidone Antagonism of Apomorphine-Induced Stereotypic Climbing in Mice

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The dopaminergic agonist apomorphine produced dose-dependent stereotypic climbing behavior in mice housed in cages with vertical bars. This drug effect was competitively inhibited by systemic pretreatment with the centrally acting dopaminergic antagonist haloperidol but not by microwave irradiation (2.45 GHz, 20 mW/cm$^2$, CW, 10 min) nor by systemic pretreatment with domperidone, a dopaminergic antagonist that only poorly penetrates the blood–brain barrier (BBB). Yet when mice were systemically pretreated with domperidone and then subjected to microwave irradiation (as above), the apomorphine effect was significantly reduced. Microwave irradiation also facilitated antagonism of the apomorphine effect by low and otherwise ineffective systemic pretreatment doses of haloperidol. Apomorphine-induced stereotypic climbing behavior was also reduced by domperidone administered intracerebrally, which bypassed the BBB. Exposure of intracerebral domperidone-pretreated animals to microwave irradiation failed to increase the degree of antagonism. These findings indicate that microwave irradiation can facilitate central effects of domperidone, a drug which acts mainly in the periphery. One possible explanation for these findings is that microwave irradiation alters the permeability of the BBB and increases the entry of domperidone to central sites of action.

**Key words: blood–brain barrier, haloperidol, central vs peripheral actions**

## INTRODUCTION

In recent years, much interest has emerged in the possible interaction of microwave radiation with biological systems. Our attention was initially drawn to this issue by reports of both microwave-induced alterations in blood–brain barrier (BBB) permeability characteristics to inert radiolabelled markers [Frey et al, 1975; Albert, 1979; Albert and Kerns, 1981] as well as alterations in central nervous system (CNS) effects of a variety of pharmacologic agents [Baranski and Edelwejn, 1968; Thomas

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and Maitland, 1979; Thomas et al, 1979, 1980; Lai et al, 1983, 1984a,b, 1986]. Unfortunately, there has been little evidence from other groups employing similar techniques to confirm either that the reported change in BBB permeability was a demonstrable phenomenon or that the reported changes in CNS activity of the pharmacologic agents were indeed due to microwave-induced alterations in BBB function [Merritt et al, 1978; Preston et al, 1979; Preston and Préfontaine, 1980].

It is highly probable that differences in animal models and microwave exposure techniques contribute to the lack of agreement on microwave-induced alterations in BBB function. However, we also felt that a more important source of disagreement lies in the relative sensitivities and specificities of the methods employed to evaluate BBB function. Two major techniques are currently employed to evaluate microwave-induced alterations of BBB function: One is histological/ultrastructural [Sutton and Nunnally, 1973; Sutton and Carroll, 1979; Albert, 1977], and the other is physiological [Crone, 1963; Oldendorf, 1970; Rapoport et al, 1978, 1979]. Both types of studies have their relative strengths and weaknesses. The histological/ultrastructural approach is highly site-specific yet lacks sensitivity, and results from such studies are difficult to quantitate. Conversely, physiological methods, although potentially extremely sensitive, usually require changes distributed over large sections of tissue to demonstrate this sensitivity.

In an effort to exploit the strengths of both techniques, we developed a pharmacological assay system, using a CNS agonist that produced a predictable behavioral response, and attempted to employ microwave radiation to alter the CNS availability of an antagonist that was normally excluded from the CNS (based on physicochemical properties). This pharmacological approach enjoyed the advantages of both sensitivity (since it was relatively easy to alter drug dose-response relationships) as well as site specificity (since the agonist/antagonist interaction had been shown to occur in a specific region of the CNS). The technique had an additional advantage in that it permitted a time-dependent evaluation of a microwave-induced response without requiring sacrifice of the test animal. Thus this report describes the influence of microwave radiation on the ability of a non-CNS-acting dopaminergic antagonist, domperidone [Laduron and Leyson, 1979], to block a drug effect of the dopaminergic agonist apomorphine, previously demonstrated to originate from a site-specific action of apomorphine on dopamine receptors in the corpus striatum of the CNS [Protais et al, 1976].

## MATERIALS AND METHODS

Over 400 male ICR mice, weighing 20–30 g, were purchased from King Animal Laboratories (Oregon, WI) for these experiments. On the day of the study, animals were acclimated for no less than 60 min to housing in individual circular cages, 12 cm in diameter and 14 cm in height, with 1 mm vertically mounted metal bars spaced 1 cm apart. These cages were additionally separated by cardboard screens to prevent any behavioral interaction between test animals. After conditioning, the animals were challenged with various doses of apomorphine and returned to their individual cages. Assessment of apomorphine-induced stereotypic climbing activity was made according to a previously published method [Quock and Lucas, 1981; Quock et al, 1983]: 0 points, the animals sits with all four paws on the cage floor; 1 point, the animal persistently stands against the cage wall with forepaws grasping the metal bars; and 2

points, the animal persistently climbs on the cage wall with all four paws grasping the metal bars. Scores were assigned by a trained observer who was not blind to the drug or apomorphine treatments; preliminary studies showed that each activity level was quite clear-cut and that prior knowledge of the treatment group did not influence the behavioral scoring. Climbing scores were assigned for two 5 min intervals ending 10 and 20 min following the apomorphine challenge, and the scores were then averaged to yield a stereotypic climbing score for each mouse. The score was determined by the most predominant behavior demonstrated during the 5 min observation period.

In experimental trials, the mice were acclimated to the circular cages, then removed for pretreatment injections followed by either microwave or sham irradiation. Animals were typically run in pairs with both mice receiving injections of the 0.9% saline solvent, haloperidol, or domperidone, then one mouse was subjected to microwave irradiation for 10 min while the other was sham irradiated at the same time. Following the exposure period, the mice were returned to their circular cages for another 20 min before the apomorphine challenge. The protocol for these systemic pretreatment experiments is illustrated in Figure 1. Each animal was used only once and then discarded.

For the purpose of microwave irradiation, we utilized a near-field waveguide microwave exposure system, constructed according to previously published specifications [Ho et al, 1973; Christman et al, 1974]. Conscious and unrestrained test animals were placed individually into a styrofoam containment chamber (5H × 9W × 11L cm) with 6 mm diameter lucite rods traversing the top and bottom of the chamber; the rods were aligned parallel to the vector of the incident electric field to permit adequate ventilation of the animals during exposure. However, unlike with the apparatus of Ho et al [1973], no attempt was made to provide forced ventilation through the exposure chamber. The styrofoam containment chamber was placed into an R-band waveguide (5.4H × 10.9W × 29L cm) modified with hinged screen doors to allow access to the interior. The waveguide was attached by coaxial cable to a 650-W microwave generator (2.45 GHz, continuous wave; CW) operating in a $TE_{10}$ mode. The microwave energy was attenuated by a model 4-5414-30 $\pi$-line attenuator

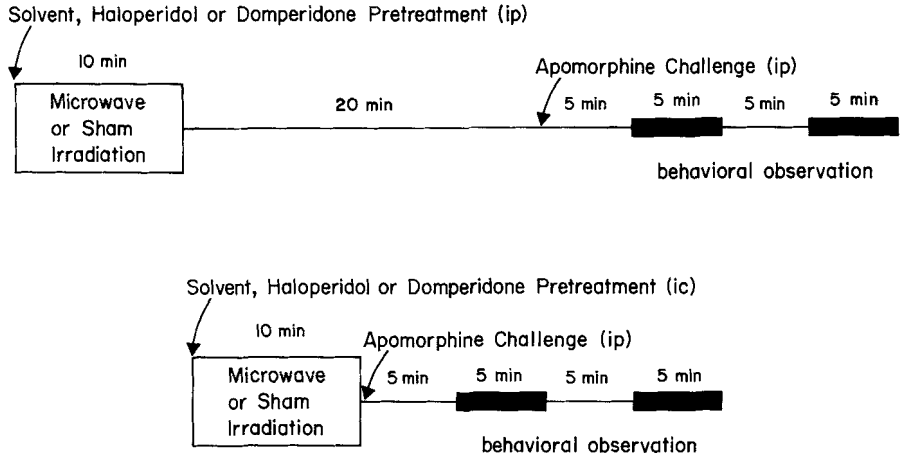


Fig. 1. Time course of experimental protocol for systemic (top) and intracerebral (bottom) pretreatment experiments.

(Arra, Bay Shore, NY), and impedence matching was accomplished using double-stub S2-15N tuners (Microlab/FXR, Livingston, NJ). Transition of the coaxial cable to the R-band waveguide exposure system was accomplished by two model R601C waveguide coaxial adaptors (Microlab/FXR). CB-67N directional couplers (Microlab/FXR) were employed to monitor incident, reflected, and transmitted power using either crystal or bolometer detectors in appropriate detector mounts in conjunction with a model 423A Hewlett-Packard power meter. The maximal power density located at the center of the containment chamber was periodically checked using a model 380m microwave leakage detector (Simpson, Elgin, IL). A specific absorption rate (SAR) of 45.5 W/kg at the nominal incidence flux of 20 $mW/cm^2$ was calculated in accordance with the Dewar-flask calorimetric technique [Blackman and Black, 1977; Durney et al, 1980] using mouse cadavers aligned parallel to the vector of the incident field. All exposures occurred at an ambient temperature of $22 \pm 1^{\circ}C$ with a relative humidity of approximately 30% in accordance with the observations of Berman et al [1985].

A separate experiment was conducted to determine if the effects of haloperidol might also be potentiated by microwave irradiation. Mice were here pretreated with 0.03 mg/kg of haloperidol, which we had determined in preliminary studies to be a subthreshold dose for antagonism of apomorphine. Animals were then exposed to microwave irradiation, and the influence on apomorphine-induced stereotypic climbing activity was assessed as described above.

Another experiment was conducted to determine if the failure of systemically administered domperidone to antagonize apomorphine was actually due to an inability to penetrate the BBB rather than reduced pharmacological activity compared to haloperidol. The 1 M lactic acid solvent (slightly acidified with glacial acetic acid), haloperidol, and domperidone were administered intracerebrally at a site approximating the lateral cerebral ventricle, thus bypassing the BBB [Haley and McCormick, 1957]. Mice were individually exposed to halothane (Fluothane; Ayerst) on small gauze pads in a large covered beaker; consciousness was lost in 15–20 sec and not regained for 2–3 min. The anesthetized mouse was removed from the beaker and a midline incision made with a scalpel to permit identification of anatomical landmarks on the calvarium. The central microinjection was made at an intracerebral depth of 2.4 mm in a volume of 4 $\mu$l slowly infused over 15–20 sec. The method was verified in nontest animals by microinjection of dye marker in similar fashion and central localization of the dye. After 10 min of either microwave or sham irradiation, mice were challenged with apomorphine and evaluated for stereotypic climbing activity (as previously described). The protocol for these intracerebral pretreatment experiments is illustrated in Figure 1.

Drugs used in this study included apomorphine HCl (Merck), haloperidol (Haldol; McNeil), and domperidone (Janssen). Apomorphine was prepared in 0.9% saline solution with one drop of 0.1 N hydrochloric acid per 10 ml of drug solution to stabilize the drug. Haloperidol was diluted to appropriate strength for injection in saline. Domperidone was prepared in 1 M lactic acid rendered slightly more acidic with glacial acetic acid; the final drug solution was titrated to pH 6–7 using 3 M sodium hydroxide. The systemic solvent, haloperidol, and domperidone pretreatments and the apomorphine challenges were all made by intraperitoneal injection in volumes of 0.01 ml/g. Intracerebral solvent, haloperidol, and domperidone pretreatments were made in a volume of 4 $\mu$l per animal.

The climbing scores of variously treated groups of animals were analyzed by the Kruskal-Wallis one-way analysis of variance by ranks and the Mann-Whitney U test [Siegel, 1956].

## RESULTS

Mice initially placed into the circular cages exhibited exploratory activity of the new environment, including varying degrees of transient cage climbing activity. However, such behavior generally subsided and disappeared after 20–30 min of acclimation. In preliminary experiments, systemic administration of solvent, haloperidol, or domperidone failed to evoke any response resembling apomorphine-induced stereotypic climbing activity in acclimated animals.

Figure 2 shows dose-response curves constructed from the systemic pretreatment experimental data. Groups of control animals challenged with three doses of apomorphine showed progressively greater mean stereotypic climbing scores: 1.0 mg/kg, 0.42 mean $\pm$ 0.10 SEM, n = 20; 2.0 mg/kg, 1.35 $\pm$ 0.08, n = 20; 3.0 mg/kg, 1.68 $\pm$ 0.12, n = 20. Each mean stereotypic climbing score was significantly different from the others ($P < 0.05$, Mann-Whitney U test). Microwave irradiation 20 min prior to apomorphine challenge had no appreciable influence on either the mean stereotypic climbing scores or the apomorphine dose-reponse curve. To demonstrate the sensitivity of this assay system to drug antagonism, the centrally acting dopaminergic antagonist haloperidol was administered at a systemic pretreatment dose of 0.1 mg/kg; this pretreatment significantly lowered the mean stereotypic climbing scores at all three challenge doses of apomorphine. In contrast, the peripherally acting dopaminergic antagonist domperidone at a systemic pretreatment dose of 1.0 mg/kg exerted no significant influence on apomorphine stereotypic climbing scores. How-

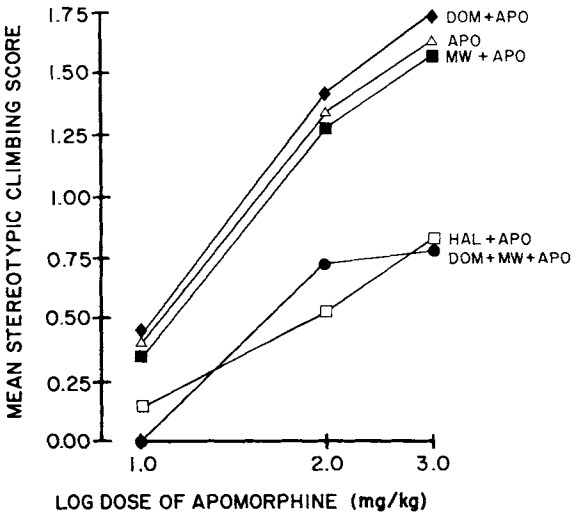


Fig. 2. Dose-response curves for apomorphine-induced stereotypic climbing activity in mice: △, control; ■, microwave-irradiated; □, haloperidol-pretreated; ♦, domperidone-pretreated mice; and ●, domperidone-pretreated and microwave-irradiated. Specific drug pretreatment doses and times and microwave exposure power densities and times can be found in the text. Points indicate the mean stereotypic climbing scores of groups of 20–28 mice each.

ever, the combination of domperidone pretreatment plus microwave irradiation, each of which alone had no effect on apomorphine, significantly reduced the mean stereotypic climbing scores at all three challenge doses of apomorphine. Although there were insufficient data to generate $pA_2$ [Arunlakshana and Schild, 1959] or even double reciprocal plots [Webb, 1963], it appeared that microwave irradiation had altered the potency of domperidone.

Table 1 shows the mean stereotypic climbing scores evoked by a single challenge dose of apomorphine (2.0 mg/kg) in mice following low-dose systemic haloperidol pretreatment with and without microwave irradiation. The data show that haloperidol at a subthreshold dose of 0.03 mg/kg produced no appreciable influence on the mean stereotypic climbing score. However, in mice pretreated with this low dose of haloperidol, then exposed to microwave irradiation for 10 min, the mean apomorphine-induced climbing score was significantly reduced. This experiment suggests that microwave irradiation can also facilitate central effects of low and otherwise inactive doses of haloperidol.

Table 2 shows the mean stereotypic climbing scores evoked by a single challenge dose of apomorphine (2.0 mg/kg) in control and intracerebrally drug-pretreated and/or microwave-irradiated mice. The data show that haloperidol at an intracerebral pretreatment dose of 1 $\mu$g significantly reduced the mean stereotypic climbing score. In comparison, domperidone at an intracerebral pretreatment dose of 3 $\mu$g also significantly reduced the mean stereotypic climbing score. Microwave irradiation of animals pretreated intracerebrally with domperidone did not alter the results obtained in the absence of microwave irradiation. Thus it did not appear that microwave exposure altered dopaminergic receptor function.

**TABLE 1. Influence of Microwave Irradiation on Haloperidol Antagonism of Apomorphine-Induced Stereotypic Climbing Behavior in Mice**

| Treatment group | N | Challenge dose of apomorphine (2.0 mg/kg) |
|---|---|---|
| Apomorphine control | 20 | 1.35 |
| Haloperidol (0.1 mg/kg, IP) + apomorphine | 25 | 0.53* |
| Haloperidol (0.03 mg/kg, IP) + apomorphine | 19 | 1.24 |
| Haloperidol (0.03 mg/kg, IP) + microwave irradiation + apomorphine | 20 | 0.85*,** |
| Kruskal-Wallis ANOVA | | 0.001 |

*Significantly different from apomorphine control group at $P < 0.05$ (Mann-Whitney U test).
**Significantly different from haloperidol (0.03 mg/kg) pretreatment group at $P < 0.05$.

**TABLE 2. Influence of Microwave Irradiation and/or Intracerebral Pretreament With Dopaminergic Antagonists on Apomorphine-Induced Stereotypic Climbing Behavior in Mice**

| Treatment group | N | Challenge dose of apomorphine (2.0 mg/kg) |
|---|---|---|
| Apomorphine control | 20 | 1.35 |
| Haloperidol (1 μg, IC) + apomorphine | 20 | 0.15* |
| Domperidone (3 μg, IC) + apomorphine | 23 | 1.03*,** |
| Domperidone (3 μg, IC) + microwave irradiation + apomorphine | 23 | 1.08*,** |
| Kruskal-Wallis ANOVA | | 0.001 |

*Significantly different from apomorphine control group at $P < 0.05$ (Mann-Whitney U test).
**Significantly different from haloperidol pretreatment group at $P < 0.05$.

## DISCUSSION

Previous reports describing the effects of microwave irradiation on BBB function and permeability characteristics have been equivocal. Findings suggestive of microwave-induced alterations in penetration of the BBB by inert radioactive tracers (sucrose or mannitol) have recently been reinterpreted actually to present alterations in cerebral blood flow [see review of Justesen, 1980]. Histological evaluations, based on protein-bound fluorescent dyes, or electron microscopic demonstration of enzyme reaction products (horseradish peroxidase) have demonstrated changes in BBB permeability, but quantitation of the results and subsequent extrapolation to physiological, pharmacological, or toxicological implications have been difficult. We have attempted to utilize the major advantageous characteristics of these two types of studies to delineate more clearly a microwave-induced alteration in BBB permeability. Thus we have developed an agonist/antagonist pharmacological assay technique that can duplicate the sensitivity of the radiotracer techniques [Oldendorf, 1970; Rapoport et al, 1978, 1979]. It shares some of the advantages of the discrete localization characteristics of histological techniques. Moreover, our assay has the distinct added advantages of monitoring an intact animal model without inducing tissue damage as well as demonstrating a pharmacologically relevant effect.

Although a number of studies have demonstrated a microwave-induced facilitation of other centrally acting pharmacologic agents [Thomas et al, 1979; Ashani et al, 1980; Benson et al, 1983], none of these studies took advantage of exogenous drug agonist/antagonist interactions. What we have attempted is the amplification of a small physiological effect by exploiting varying receptor affinities and/or availabilities for a centrally mediated agonist/antagonist interaction. Systemic challenge with the lipophilic agonist apomorphine permits rapid entry into the CNS without significant effects or changes in capillary endothelial cell permeability characteristics, since its uptake into the CNS is predominantly a function of its lipophilicity. Conversely, the systemic administration of the hydrophilic antagonist domperidone results in minimal penetration of the compound into the CNS, which results in maximal sensitivity to changes in capillary endothelial cell permeability characteristics. Thus we were able to monitor selectively the effects of altered BBB permeability on the CNS availability

of the antagonist. In addition, if the relative affinity of the antagonist is significantly greater than that of the agonist, we should be able to amplify greatly the behavioral response of the animal model to the agonist/antagonist interaction.

In the present investigation, the interaction between apomorphine and domperidone was selected for the following reasons. Apomorphine has clearly been shown to produce site-specific activation of dopaminergic receptors in the corpus striatum to evoke stereotypic climbing behavior [Protais et al, 1976]. Suppression of apomorphine-induced stereotypic climbing has in fact been popularly used as a screen for identification of drugs with potential neuroleptic activity [Costall et al, 1978; Wallach et al, 1980]. Domperidone has been demonstrated to possess a dopaminergic receptor blocking property, yet it does not readily penetrate the BBB, so its activity is largely restricted to the periphery [Laduron and Leysen, 1979]. Previous studies have shown that domperidone and haloperidol have similar $IC_{50}$ values (5 nM) for displacement of $^3$H-apomorphine in rat brain striatal tissue [Leysen, 1980]. However, domperidone is distributed in the CNS differently from classical neuroleptic agents [Laduron and Leysen, 1979]. Following peripheral administration, its duration of action is as long as 16 hr [Farah et al, 1983]. Thus using this unique combination of apomorphine and domperidone in our particular assay system fulfilled our requirements and has the potential for demonstrating microwave-induced alterations in BBB function.

Our findings in the present study show clearly that domperidone possessed central dopaminergic antagonistic properties normally not manifested because of its failure to penetrate the BBB. When domperidone is systemically administered, there is no change in apomorphine-induced stereotypic climbing. Microwave irradiation of systemic domperidone-pretreated animals produces significant antagonism of apomorphine by domperidone, comparable to the haloperidol-pretreated animals. This finding suggests an increase in the CNS availability of domperidone in microwave-irradiated animals. When domperidone is intracerebrally administered—bypassing the BBB—the apomorphine drug effect is markedly reduced, which verifies the inherent dopaminergic antagonistic property of domperidone. Microwave irradiation of the intracerebral domperidone-pretreated animals failed to increase the antagonism of the apomorphine drug effect. This suggests that the site of the microwave influence is not at the level of the dopaminergic receptor.

Our findings also indicate that microwave exposure can increase the antagonism of apomorphine drug effects by both haloperidol (at low concentrations) and domperidone. This observation suggests that haloperidol and domperidone share some common mechanism for gaining accessibility to the CNS since the apparent availability of each is enhanced by microwave irradiation.

One possible mechanism by which microwave irradiation could alter the CNS availability of exogenously adminstered drugs is through a change in the cerebral blood flow [Oscar and Hawkins, 1977; Preston et al, 1979; Oscar et al, 1981]. The CNS availability of exogenous compounds with low extraction coefficients, such as domperidone, is not dependent on tissue perfusion rates as demonstrated by in vivo studies [Wilkinson and Schand, 1975; Benson et al, 1983; Quock et al, 1986; Eger, 1974] and by mathematical models [Papenfuss and Gross, 1980]. These studies support the hypothesis that the increase in cerebral blood flow, secondary to the hyperthermic response to microwave irradiation, is not responsible for our observation of altered potency of domperidone. However, until the converse hypothesis is tested, the possibility of altered cerebral blood flow participating in our observations cannot be excluded.

Other investigators have also studied the influence of microwave irradiation on brain dopaminergic systems. Microwave irradation has been reported to augment apomorphine-induced hypothermia and stereotyped behavior in rats [Lai et al, 1983]. This is at first glance inconsistent with our findings, which showed no influence of microwave irradiation on apomorphine-induced stereotypic climbing activity. However, in the Lai et al study, rats were exposed to 1 $mW/cm^2$ of microwave irradiation for 45 min immediately prior to apomorphine challenge, whereas our mice were exposed to 20 $mW/cm^2$ of microwave irradiation for 10 min, ending 20 min before the apomorphine challenge. Since microwave-induced changes in permeability of the BBB are thought to be reversible in nature, it is possible that the potential for enhancement of the apomorphine drug effect in our mice had dissipated by 20 min after irradiation. However, other investigators have reported partial reversibility of the microwave effect on the BBB after 60 min [Oscar and Hawkins, 1977; Albert and Kerns, 1981].

In summary, our findings clearly demonstrate that exposure to microwave radiation can alter the CNS potency of systemically applied agents. This facilitation of apomorphine antagonism by domperidone appeared to be secondary to an alteration in CNS availability, which by experimental design was insensitive to microwave-induced alterations in cerebral blood flow. Microwave irradiation did not alter the central activity of domperidone by influencing its interaction with dopaminergic receptors, since direct intracerebral domperidone pretreatment was insensitive to potency changes following exposure to microwave radiation. Although histological evidence of altered capillary endothelial cell tight-junction dysfunction cannot be disclaimed at an SAR of 45.5 W/kg (20 $mW/cm^2$ near field), we have preliminary data demonstrating no alteration in tight-junction integrity at 23.7 W/kg (10 $mW/cm^2$ near field) in a similar agonist/antagonist interaction paradigm [Quock et al, 1986]. We believe that the most probable explanation for our observation of microwave-induced alteration in BBB permeability to domperidone is through a stimulation of micropinocytotic activity, as previously postulated by other investigators [Albert and Kerns, 1981]. However, additional confirmatory evidence must be achieved before this hypothesized mechanism can be successfully defended.

One final issue that must be addressed is the stimulus produced by the exposure to microwave radiation. Presently, it is proposed that our observations are secondary to a thermal response of the organism to the applied microwave field. Although the alteration in core body temperature, above control animals, is usually within the diurnal temperature fluctuation range of mice ($\pm 1.0$ °C) for exposure power of 20 $mW/cm^2$ for 10 min or less, it is obvious from the SAR data that a significant thermal stress had been applied in our animal model. Currently, we are investigating alternative thermal application techniques to evaluate the possibility that microwave irradiation, because of its relatively unique pattern of energy deposition in vivo, is much more effective at producing change in CNS micropinocytotic activity than other stimuli. This clearly appears to be the case in other organ systems but remains to be clarified in CNS capillary endothelial cells.

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