

Permeability of the Blood-Brain Barrier Induced by 915 MHz Electromagnetic Radiation, Continuous Wave and Modulated at 8, 16, 50, and 200 Hz

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ABSTRACT Biological effects of electromagnetic fields (EMF) on the blood-brain barrier (BBB) can be studied in sensitive and specific models. In a previous investigation of the permeability of the blood-brain barrier after exposure to the various EMF-components of proton magnetic resonance imaging (MRI), we found that the exposure to MRI induced leakage of Evans Blue labeled proteins normally not passing the BBB of rats [Salford et al. (1992), in: *Resonance Phenomena in Biology*, Oxford University Press, pp. 87–91].

In the present investigation we exposed male and female Fischer 344 rats in a transverse electromagnetic transmission line chamber to microwaves of 915 MHz as continuous wave (CW) and pulse-modulated with repetition rates of 8, 16, 50, and 200 s⁻¹. The specific energy absorption rate (SAR) varied between 0.016 and 5 W/kg.

The rats were not anesthetized during the 2-hour exposure. All animals were sacrificed by perfusion-fixation of the brains under chloral hydrate anesthesia about 1 hour after the exposure. The brains were perfused with saline for 3–4 minutes, and thereafter fixed in 4% formaldehyde for 5–6 minutes. Central coronal sections of the brains were dehydrated and embedded in paraffin and sectioned at 5 µm. Albumin and fibrinogen were demonstrated immunohistochemically.

The results show albumin leakage in 5 of 62 of the controls and in 56 of 184 of the animals exposed to 915 MHz microwaves. Continuous wave resulted in 14 positive findings of 35, which differ significantly from the controls ($P = 0.002$). With pulsed 915 MHz microwaves with repetition rates of 200, 50, 16, and 8 s⁻¹, 42 of 149 were positive, which is highly significant at the $P = 0.001$ level. This reveals that both CW and pulsed 915 MHz microwaves have the potential to open up the BBB for albumin passage. However, there is no significant difference between continuous and pulsed 915 MHz microwaves in this respect.

The frequency of occurrence of extravasates (26%) was found to be independent of SAR for SAR < 2.5 W/kg, but rose significantly for the higher SAR values (to 43%).

The question of whether the opening of the blood-brain barrier constitutes a health hazard demands further investigation. © 1994 Wiley-Liss, Inc.

INTRODUCTION

The mammalian brain is protected from potentially harmful compounds in the blood by the so-called blood-brain barrier (BBB) a selectively permeable, hydrophobic barrier that is readily crossed by small, lipid-soluble molecules (Oldendorf, 1975; Rapoport, 1976). Certain lipid-insoluble molecules such as glucose also readily cross the cell layers constituting the barrier via carrier proteins that have a high affinity to specific molecules.

Although knowledge of the barrier's adaptive role is far from complete, there is a growing consensus that it serves not only to restrict entry of toxic polar molecules into the brain but also as a regulatory system that stabilizes and optimizes the fluid environment of the

brain's intracellular compartment (Oldendorf, 1975; Rapoport, 1976).

The intact BBB protects the brain from damage, whereas a dysfunctioning BBB, as induced by epileptic seizures or extreme hypertension, allows influx of normally excluded hydrophilic molecules into the brain tissue. This might lead to cerebral edema, increased intracranial pressure, and, in the worst case, irreversible brain damage.

The normal selective permeability of the BBB can be

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altered in several neuropathological conditions and experimental situations. The BBB is opened during an acute hypertensive episode (Sokrab et al., 1988a,b), in epileptic seizures (Mihaly and Bozoky, 1984), and during therapeutic X-ray irradiation (Nair and Roth, 1964).

Several authors have reported that electromagnetic exposure alters BBB permeability (Albert, 1977; Albert et al., 1978; Ashani et al., 1980; Garber et al., 1989; Lin and Lin, 1980, 1982; Oscar and Hawkins, 1977; Prato et al., 1990; Sutton and Carroll, 1979; Sutton et al., 1973). Other authors have reported difficulties in confirming these findings (Merritt et al., 1978; Preston and Prefontaine, 1980; Preston et al., 1979; Spackman and Riley, 1978; Williams et al., 1984a-d). The lack of agreement among investigators might be due to lack of an assay of BBB permeability that combines sensitivity and specificity.

Shivers et al. (1987) observed an amplified vesicle-mediated transport of horseradish peroxidase across the endothelium to the extracellular compartment of the brain parenchyma of the rat during exposure to clinical magnetic resonance imaging (MRI) procedures. They did not, however, report on effects of the exclusive field components. The mechanism involved points strongly to a stimulation of a pinocytotic-like transport of albumin through the BBB. (Neubauer et al., 1990).

In a previous investigation we have studied the permeability of the BBB after exposure to the components of the MRI electromagnetic fields: static magnetic fields (SMF), low-frequency pulsed magnetic fields (TVMF), radiofrequency electromagnetic fields (RF), and a combination of the three types of fields. We found that the exposure to MRI induced leakage of proteins that do not normally pass the BBB (Salford et al., 1992).

The BBB seems to be a sensitive and specific model for the study of biological effects of electromagnetic fields (EMF) on human tissue. We therefore chose this model for a systematic study of the repetition rate and intensity dependence of biological reactions by exposure to pulsed radiofrequency radiation.

In the present investigation we studied the permeability of BBB to endogenous albumin and fibrinogen during exposure to microwaves of 915 MHz as continuous wave (CW) and pulse-modulated at the various repetition rates (8–200 s⁻¹). Preliminary results were reported by Salford et al. (1992).

MATERIALS AND METHODS

Exposure in a TEM Cell

A transverse electromagnetic transmission line cell (TEM cell) used for the RF exposure of rats was designed by dimensional scaling from previously constructed cells at the National Bureau of Standards (Crawford, 1974). TEM cells are known to generate uniform TEM fields for standard measurements

The cell is enclosed in a wooden box that supports the outer conductor and central plate. The outer conductor is made of brass net and is attached to the inner walls

of the box. The center plate, or septum, is constructed of aluminium and is held up by Teflon braces that are screwed at the inner side walls.

To allow access to the inside of the cell, both ends can be removed. The inside of the cell is ventilated through 18 holes (diameter, 18 mm) in the side walls and top of the box, and the brass net allows air to circulate. These holes are also used for examination of the interior during exposure. Probes for monitoring temperature inside the cell or test object are inserted through these holes.

The rate of electromagnetic energy absorbed in tissue per unit mass is called specific absorption rate (SAR) and is given by the expression (Hand, 1990)

$$\text{SAR} = \sigma E^2 / 2\rho$$

where E is the electrical field in the tissue, in units of V/m, σ is the electrical conductivity in units of siemens/meter ($\sigma = 0.9$ S/m in the rat brain (Lin, 1986), and ρ is the density of the tissue in kg/m³.

Table 1 lists the number of rats exposed to 915 MHz electromagnetic radiation at different intensities and pulse-modulated with different repetition rates. The modulated RF radiation consists of square wave-shaped pulses with durations of 0.57, 4, or 6 ms and intensities (in Watts) during the presence of the pulse as indicated in the table. The SAR value in the rat brain for each experimental condition is also listed. These SAR values are based on a crude estimate using the E -field in the TEM-cell (Crawford, 1974) as the internal field in the rat brain.

In order to be able to calculate accurate SAR values in the rat brain, the E -field distribution in the brain must be known. In the ideal TEM cell, a uniform plane electromagnetic wave propagates through the cell. If a structure is placed in a TEM cell, the incident wave is partially reflected and partially refracted and absorbed. Complications in the modeling of the fields in the structure arise from the facts that: 1) the transverse electromagnetic wave (TEM wave) is not completely uniform over the volume of the cell; and 2) the electromagnetic field distribution in the cell will be perturbed by the presence of the structure.

Martens et al. (1992) have performed calculations of three-dimensional electromagnetic fields for our TEM cell that contains an inhomogeneous structure, using the finite difference time domain (FDTD) method. The E -distribution in any irregular shaped, inhomogeneous structure placed in the TEM cell can be calculated with this method (Martens et al., 1992; Van Hese et al., 1992). SAR distributions in the brain of rats, placed in the upper and lower compartments of our TEM cell and averaged over different orientations with respect to the incident electromagnetic wave, will be published elsewhere.

Albumin and Fibrinogen Immunohistochemistry

Fischer 344 rats, 106 male and 140 female, weighing between 119 and 555 g (median: 202 g; 25% quartile: 175 g; 75% quartile: 273 g) were used in these experiments (own breeding). The rats were not anesthetized during the 2-hour exposure.

TABLE 1. Number of animals and specific absorption rate (SAR) for each experimental condition for pulsed 915 MHz radiofrequency radiation with different repetition rates and pulse widths

Repetition rate (s ⁻¹):	8	16	50	200	CW
Pulse width (ms):	0.57	0.57	4	0.57	
Power in pulse (W)	No. of animals investigated at repetition rate/pulse width (SAR in W/kg)				
0.2					6 (0.3)
1			9 (0.3)		2 (1.7)
2	6 (0.016)	8 (0.03)	6 (0.7)	18, 6 ¹ (0.4, 2.9) ¹	6 (3.3)
3					21 (5.0)
5	6 (0.04)	6 (0.08)	6 (1.7)	6 (1.0)	
10	8 (0.08)	6 (0.15)	12, 2 ² (3.3, 5.0) ²	8 (2.1)	
20	12 (0.16)	12, 6 ¹ (0.3, 2.1) ¹	6 ³ (1.0) ³		

¹Pulse width 4 ms.²Pulse width 6 ms.³Pulse width 0.57 ms.

TABLE 2. Summary of findings of albumin extravasates through the blood-brain barrier after exposure to 915 MHz electromagnetic fields, continuous and pulse-modulated with various repetition rates

Pulse rate (s ⁻¹)	No. of rats with extravasation ¹			
	0	(x)	(xx)	Total
8	24	8	0	32
16	28	10	0	38
50	27	12	2	41
200	28	10	0	38
CW	21	13	1	35
Control	57	5	0	62

¹0, no or occasional artefactual staining; x, one to three extravasates per cross section of the brain; xx, four or more extravasates per cross section of the brain. Size of extravasate 15–100 μ m.

All animals were sacrificed by perfusion-fixation of the brains under chloral hydrate anesthesia between 20 minutes and 2 hours after the exposure. The brains were perfused with saline for 3–4 minutes, thereafter fixed in 4% formaldehyde for 5–6 minutes, and immersion fixed in 4% formaldehyde for more than 24 hours. Central coronal sections of the brains (3, 7, and 11 mm from the tip of the frontal pole) were dehydrated and embedded in paraffin and sectioned at 5 μ m.

Albumin was demonstrated with the IgG fraction of rabbit anti-rat albumin (Cappel Research Products, Organon Teknika, Västra Frölunda, Sweden) diluted 1:16,000. Fibrinogen was demonstrated with rabbit anti-human fibrinogen (Dacopatts AB, Hägersten, Sweden), diluted 1:500. Incubation time for both was over night at 4°C.

Biotinylated swine anti-rabbit IgG was used as a secondary antibody. Then avidin, peroxidase conjugated, was coupled to the biotin and visualized with diaminobenzidine (DAB), counterstained with Meyer-HTX (Dacopatt Handbook of Immunochemical Staining Methods). Standard control procedures were used for both albumin and fibrinogen.

Statistics

The frequency of occurrence of albumin extravasation in exposed and control animals was compared with chi-square or Fischer's exact probability test.

RESULTS

The unanesthetized animals accepted the stay in the TEM cells without signs of distress. The immunohistochemical technique employed seems to be both sensitive and specific in detecting extravasations in the brains of exposed animals.

Demonstration of albumin was regularly positive in normally BBB weak areas like surface membranes, choroid plexus, pituitary stalk, and hypothalamus. There were also rather frequent positive findings in the central parts around the third ventricle. Positive findings were also found bilaterally within dorsolateral parts and the thalamus and adjacent inferior aspects of the hippocampus, all with a rather symmetric distribution. These were the findings in control animals and were seen as a background to additional positive findings in test animals.

Apart from the positive findings in traditionally BBB weak areas, in test animals extravasation of albumin was also found in the semioval center on both sides, joined by the callosal body. This might be due to the spread within this tract system from a focus anywhere within these structures. This type of finding was regarded as pathological, as were some other positive areas also located outside the BBB weak areas such as in the cortex, lateral thalamus, etc. The albumin extravasation was asymmetrical and spotty (Fig. 1a–c) often centered around small vessels (Fig. 2c). There was no immunopositive response for fibrinogen. Leakage of albumin was often taken up by glial and neuronal cells in the vicinity of a capillary (e.g., Fig. 2b). These findings, but particularly those that were asym-

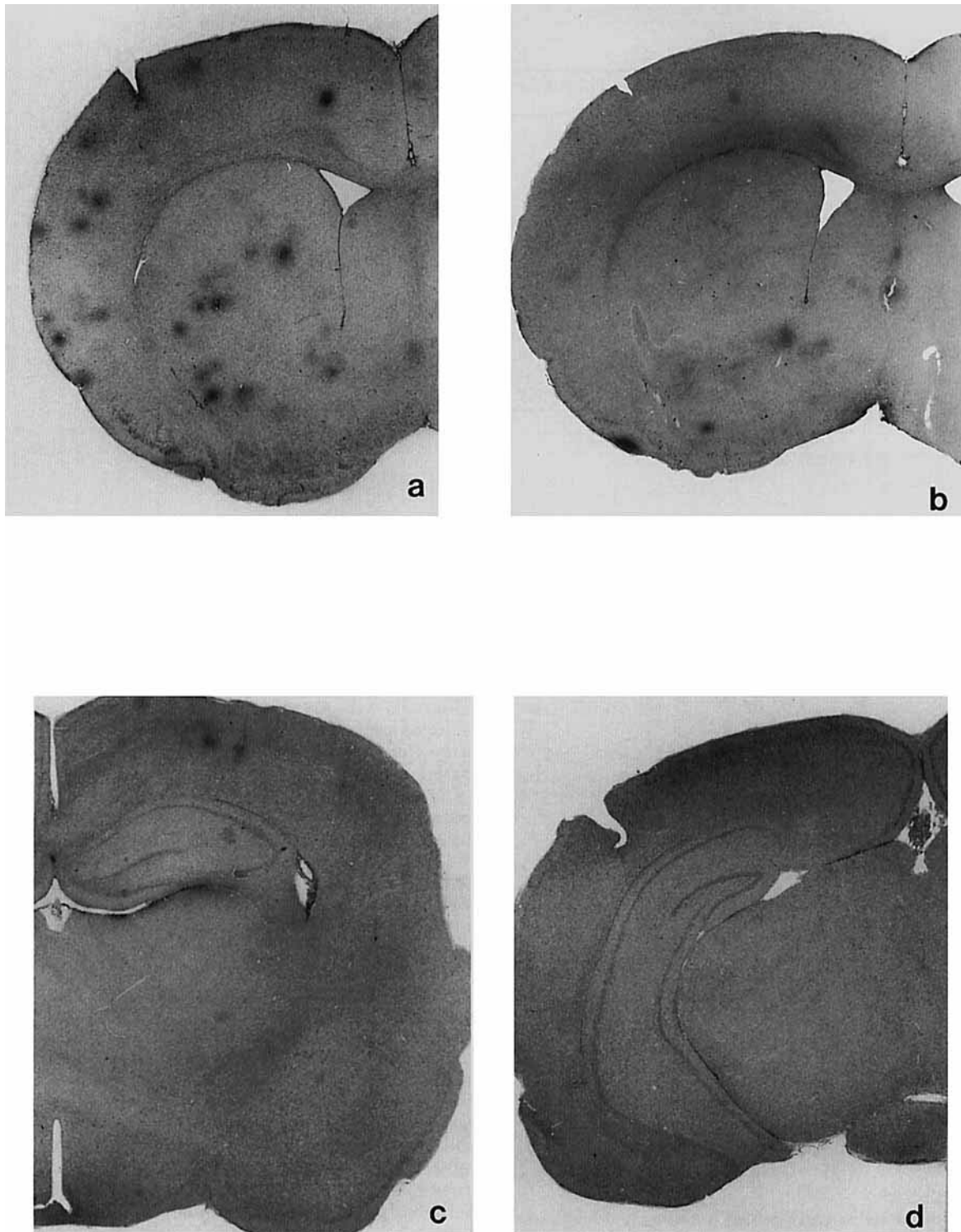


Fig. 1. Overview of one rat hemisphere in a coronal section, immunostained for albumin and counter-stained with cresyl violet. **a:** Exposure to pulsed RF radiation with repetition rate 50 s^{-1} , 10 W/pulse ($\text{SAR} = 3.3 \text{ W/kg}$) has resulted in numerous areas of albumin leakage appearing as spotty dark areas. **b:** Pulse rate 200 s^{-1} , 2

W/pulse ($\text{SAR} = 0.4 \text{ W/kg}$) produced fewer and less distinct areas of leakage, here mainly in the basal portions of the brain. **c:** Continuous radiation, 0.2 W ($\text{SAR} = 0.33 \text{ W/kg}$) resulted in a few areas of albumin leakage in the top part of the section. **d:** Control animal showing no signs of albumin leakage. Magnification $\times 13$.

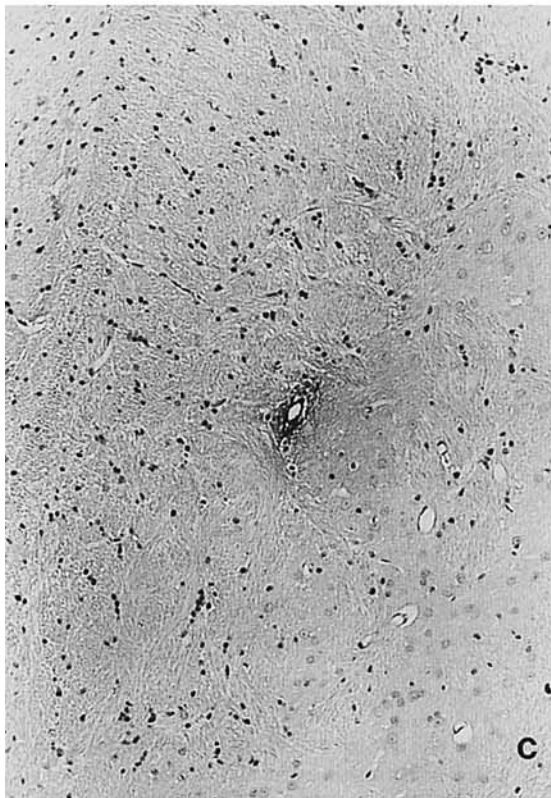
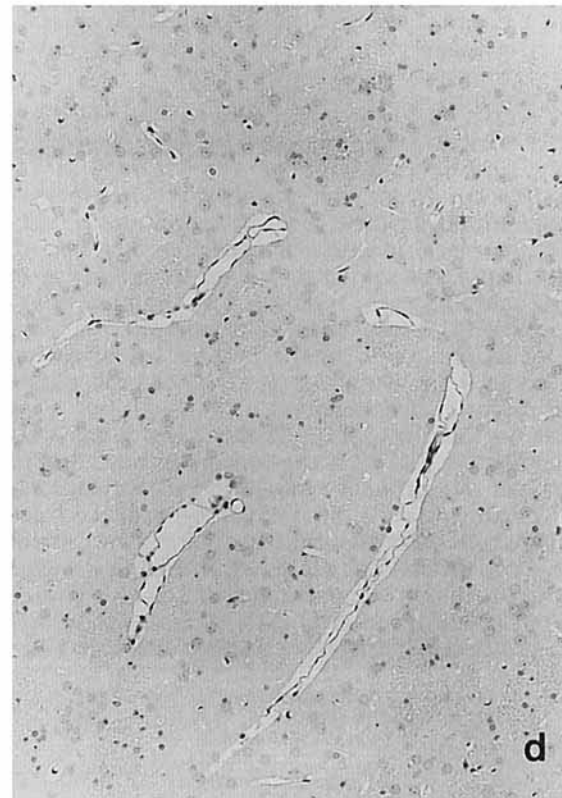


Fig. 2. Higher magnification ($\times 110$) of areas in animals shown in Figure 1, treated with the same methods. **a:** ($50 \text{ s}^{-1}/10 \text{ W/pulse}$) shows rather densely crowded foci of leakage of varying intensity. **b:** ($200 \text{ s}^{-1}/2 \text{ W/pulse}$) reveals two discrete foci of leakage with uptake of

albumin in neurons. **c:** (CW/0.2 W) depicts central vessel surrounded by immunopositive area fading out towards the periphery. **d:** Control animal with no albumin extravasation.

TABLE 3. Odds ratio for the frequency of occurrence of albumin extravasates after exposure to 915 MHz electromagnetic fields as a function of pulse rate as compared with the control animals (all SAR values pooled)

Exposure condition	Frequency $N_{\text{pos}}/N_{\text{tot}}$		Odds ratio	Significance test exposed/control (<i>P</i> value)
	Ratio	(%)		
8 s ⁻¹ 2	8/32	25	3.1	0.02
16 s ⁻¹ 2	10/38	26	3.3	0.01
50 s ⁻¹ 2	14/41	34	4.2	0.001
200 s ⁻¹ 2	10/38	26	3.3	0.01
CW	14/35	40	5.0	0.002
Σ pulse-modulated	42/149	28	3.5	0.0014
Σ CW + pulse-modulated	56/184	30	3.8	0.0004
Σ pulse-modulated ³			0.7 ³	0.17 ³
Control	5/62	8	1	

¹Positive (pos) includes x and xx (see Table 2 for explanation).

²Repetition rate.

³As compared with continuous wave (CW).

TABLE 4. Summary of findings of albumin extravasates through the blood-brain barrier after exposure to 915 MHz electromagnetic fields as a function of specific absorption rate (SAR)

SAR [W(kg)]	No. of rats with extravasation			
	0 ¹	x ¹	xx ¹	Total
0 (controls)	57	5	0	62
0.016–0.1	25	9	0	34
0.1–0.4	30	13	1	44
0.4–2	35	10	0	45
2–4	25	9	2	36
4–5	13	12	0	25
Total no. of rats	185	58	3	246

¹See Table 2 for explanation.

metrically positive, were regarded as carrying particular weight in this context.

Two types of analyses were performed: 1) a cross tabulation of number of rats with positive findings as function of pulse repetition rate, irrespective of exposure intensity, expressed as Watts during the presence of the pulse; and 2) a cross tabulation as function of exposure intensity, irrespective of repetition rate. The number of animals used in the present investigation did not allow a simultaneous analysis of both pulse-rate and intensity dependencies.

The results summarized in Tables 2 and 3 show albumin leakage in 5 of 62 of the control animals and in about 30% of the animals exposed to 915 MHz microwaves. Continuous wave resulted in 14 positive findings of 35, which differed significantly from the control animals ($P = 0.002$). With pulsed 915 MHz microwaves at 200, 50, 16, and 8 s⁻¹ repetition rates, 42 of 149 were positive, resulting in an odds ratio (OR) of OR = 3.5, which is highly significant ($P = 0.0014$). The odds ratio is defined as:

$$\text{OR} = \frac{(N_{\text{pos}}/N_{\text{tot}})_{\text{Exposed}}}{(N_{\text{pos}}/N_{\text{tot}})_{\text{Controls}}}$$

where $N_{\text{pos}}/N_{\text{tot}}$ = frequency of occurrence of positive findings within a group of animals. In the above results, positive findings of different severity classes (see

Table 2, footnote 1, for an explanation) were pooled. The tables reveal that both CW and pulsed 915 MHz microwaves have the potential to open the BBB for albumin passage. However, there is no significant difference between continuous and pulsed 915 MHz microwaves in this respect (Table 3).

A simultaneous statistical test for differences in response as function of pulse repetition rate (including CW; repetition rate ∞) allowed rejection of the null hypothesis with $P = 0.0008$, whereas the same test with the control animals excluded, revealed that the frequency of positive findings is independent of pulse repetition rate ($P = 0.59$).

Table 4 shows the number of animals with extravasations as a function of estimated SAR value. Statistical testing reveals the following (Table 5). A simultaneous test of the six SAR groups according to Table 5 (including controls) shows that the OR is SAR dependent ($P = 0.003$). The same test excluding controls fails to show any difference in response between the different SAR groups, the ORs being about 3, except for the highest SAR group, which has OR = 6.0 (Table 5). When the exposed animals are divided into two groups, low-SAR and high-SAR, a difference in response is detected if the discriminating SAR value is chosen to be 2.5 W/kg [OR(low) = 3.3, OR(high) = 5.3; $P = 0.04$].

Thus it can be concluded that:

1. Exposed animals are at risk concerning opening of the BBB (OR = 3.8; $P = 0.0004$).

2. The response is independent of pulse repetition rate, and the response is the same for CW as compared with pulse modulation.

3. The response is independent of SAR in the interval 0.016 < SAR < 2.5 W/kg (OR = 3.3), but rises for SAR > 2.5 W/kg.

DISCUSSION

During the progress of our experiments, we found that the immunohistochemical methods for albumin and fibrinogen are superior to the use of Evans Blue in revealing BBB leakage. The immunohistochemical methods allow for the identification of even minor leakage of protein and give an exact histological localiza-

TABLE 5. Odds ratio and 95% confidence interval for the frequency of occurrence of albumin extravasates for different SAR values as compared with control animals (all pulse repetition rates pooled)

SAR (W/kg)	No. in group	Frequency extravasates (%)	Odds ratio	95% Confidence interval	P value
Controls	62	8	1		
0.016–0.1	34	26	3.3	1.3–8.6	0.015
0.1–0.4	44	32	3.9	1.7–9.1	0.002
0.4–2	45	22	2.8	1.05–7.4	0.04
2–4	36	31	3.3	1.5–7.1	0.002
4–5	25	48	6.0	2.6–13.6	< 0.0001

tion of this leakage. Such methods have never before been applied to studies of EMF effects on the BBB.

The immunohistochemical method is superior to methods that use the detection of radioactive tracers in the brain, as these methods only measure tracer "space" in the brain and therefore only indirectly BBB permeability. Also these methods require injection of tracers and anesthesia during exposure.

The leakage seems to stem from vessels around which it was often seen to be centered. If not centered around a vessel, the leakage may be due to sectioning through the periphery of areas of leakage or through areas with albumin flow along tracts of the white matter, far from the vessel of origin.

The fact that the larger fibrinogen molecules (400,000 kD as compared with albumin, 69,000 kD) do not pass the BBB in any experimental condition examined indicates that the impact of EMF on the BBB is of limited effect. Thus the combined examination for albumin and fibrinogen extravasation provides a good tool for grading the influence of EMF upon the BBB.

Our conclusion is that the previously demonstrated effect upon the BBB by the radiation components of an MRI exposure is also found at 915 MHz exposure. The effect was shown for continuous radiation and for radiation pulsed with repetition rates of 8, 16, 50, or 200 s⁻¹ and estimated SARs as low as 0.016 W/kg. The number and size of extravasates in the rat brain did not seem to be correlated to either pulse repetition rate or SAR. However, the relative number of animals showing extravasates was higher for SAR > 2.5 W/kg than for the group with SAR between 0.016 and 2.5 W/kg. Thus it seems reasonable to assume that the extravasations are induced, at least partly, by a non-thermic type of interaction with the electromagnetic field. Whether the higher frequencies of extravasate findings found in this investigation for SAR > 2.5 W/kg are a thermal effect, as suggested by Moriyama et al. (1991), demands supplemental studies on dose-response relationships. Questions about the lower exposure limit for non-thermal opening of the BBB, the effects of long-term exposure, and whether the opening of the BBB constitutes a health hazard demand further investigation.

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