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# Blood-Brain Barrier Permeability and Nerve Cell Damage in Rat Brain 14 and 28 Days After Exposure to Microwaves from GSM Mobile Phones

JACOB L. EBERHARDT<sup>1</sup>, BERTIL R. R. PERSSON<sup>1</sup>,  
ARNE E. BRUN<sup>2</sup>, LEIF G. SALFORD<sup>3</sup>, AND  
LARS O. G. MALMGREN<sup>4</sup>

<sup>1</sup>Department of Medical Radiation Physics, Lund University Hospital, Lund, Sweden

<sup>2</sup>Department of Neuropathology, Lund University, Lund, Sweden

<sup>3</sup>Department of Neurosurgery (The Rausing Laboratory), Lund University, Lund, Sweden

<sup>4</sup>MAX-Lab, Lund University, Lund University, Lund, Sweden

*We investigated the effects of global system for mobile communication (GSM) microwave exposure on the permeability of the blood-brain barrier and signs of neuronal damage in rats using a real GSM programmable mobile phone in the 900 MHz band. Ninety-six non-anaesthetized rats were either exposed to microwaves or sham exposed in TEM-cells for 2 h at specific absorption rates of average whole-body Specific Absorption Rates (SAR) of 0.12, 1.2, 12, or 120 mW/kg. The rats were sacrificed after a recovery time of either 14 or 28 d following exposure and the extravasation of albumin, its uptake into neurons, and occurrence of damaged neurons was assessed. Albumin extravasation and also its uptake into neurons was seen to be enhanced after 14 d (Kruskal Wallis test:  $p = 0.02$  and  $0.002$ , respectively), but not after a 28 d recovery period. The occurrence of dark neurons in the rat brains, on the other hand, was enhanced later, after 28 d ( $p = 0.02$ ). Furthermore, in the 28-d brain samples, neuronal albumin uptake was significantly correlated to occurrence of damaged neurons (Spearman  $r = 0.41$ ;  $p < 0.01$ ).*

**Keywords** Rats; CNS; Blood-brain barrier; Neuronal damage; Microwaves; Mobile phones.

## Introduction

The availability and usage of mobile phones is still increasing. The technology is accessible to everyone, everywhere, which means that most people are exposed to its microwaves, either by choice or passively. Furthermore, it is not just the increase in the number of users, but the frequency of exposure occasions and amount of time

Address correspondence to Jacob L. Eberhardt, Department of Medical Radiation Physics, Lund University Hospital, S-221 85 Lund, Sweden; E-mail: Jacob.Eberhardt@med.lu.se

spent using a mobile phone has also increased. Yet, very little is known about any adverse health effects from its electromagnetic radiation. Exposure may consist of either chronic, extremely low-intensity whole body irradiation from base stations, and/or of acute irradiation at higher intensities of part of the body from the phones. The target organ at risk will also vary with respect to the type and nature of the exposure. Some recent epidemiological studies indicate that long-term exposure might increase the risk for some tumor forms but at the same time other reports dispute these findings, giving rise to controversy (Kundi et al., 2004; Moulder et al., 2005).

For the past 25 years, we have been studying the effects from exposure to electromagnetic fields, in both continuous wave forms and those used in the global system for mobile communications (GSM), on rat brain. We have shown that the blood-brain barrier (BBB), which normally strictly controls the transport of substances from the general blood circulation into and out of the brain, becomes less selective after exposure to microwaves. This was shown by the abnormal presence of endogenous albumin in the brain tissue after exposure to 900 MHz microwaves on just one single occasion (Persson et al., 1997; Salford et al., 1993, 1994). Albumin is a relatively small molecule, so it is conceivable that other substances also have access to the brain after microwave exposure, leading to an immediate primary, reversible, or irreversible adverse effect and then, through a cascade of maybe secondary events, to longer-lasting permanent changes in the brain. Alternatively, albumin can form adducts with other xenobiotics and function as a carrier molecule, leading again to any of the above-mentioned effects.

According to Shivers et al. (1987), the mechanism behind the BBB-leakage is an active, vesicle-mediated transport through the blood vessels endothelial cells (pinocytosis). The membranes of other neuronal cell organelles such as mitochondria and lysosomes of the residual body type also may be affected. This can be hypothesized to release or initiate aggressive-free radicals and further may release previously sequestered residual body material including heavy metals and peroxidized lipid membrane residues. This would mean that potentially harmful substances may emanate not only from the blood but also from endogenous sources.

Back in 1973, Tolgskaya and Gordon described morphological changes in brains of rats after long-term exposure to low intensities of microwaves (Tolgskaya and Gordon, 1973). The opening of the BBB by mobile phone radiation has been shown by other researchers. In Fritze et al. (1997) and Töre et al. (2001), opening of the BBB were seen in both thermal and non thermal regions of Specific Absorption Rate (SAR), while in another study no such effect was seen (Tsurita et al., 2000).

Additional support for our findings that low-intensity GSM 900 MHz electromagnetic fields influence the BBB is provided by the in-vitro proteomic studies on a human endothelial cell line by Leszczynski et al. (2002) and Nylund and Leszczynski (2006). Recent findings show that microwave radiation with SAR values of 15–20 mW/kg induces albumin denaturation and promotes amyloid fibril formation (de Pomerai et al., 2003). In one of our previous studies (Salford et al., 2003), we reported on neuronal damage in rat brain seen 50 d after a single 2-h exposure to GSM-900 radiation with SAR values between 2 and 200 mW/kg.

The aims of the present study are:

- i) to follow the presence and distribution of albumin in rat brain (albumin foci, diffuse occurrence of albumin, and albumin uptake into neurons);
- ii) to follow the development and progression of neuronal damage in more detail; and

- iii) to investigate the effects of an even lower exposure level ( $\text{SAR} = 0.12 \text{ mW/kg}$ ) in a rat model after a recovery time of 14 and 28 d after a single 2-h exposure to 900 MHz radiation from GSM.

## Materials and Methods

Note: All animal procedures were performed according to the practices of the Swedish Board of Animal Research and were approved by the Animal Ethics Committee, Lund-Malmö.

The Transverse Electromagnetic transmission line cell (TEM-cell) used for the radio frequency (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 electromagnetic fields for standard measurements. A genuine GSM mobile phone with a programmable power output is connected via a coaxial cable to the TEM-cell. No voice modulation was applied. For a description of the TEM-cell, see Malmgren (1998).

The TEM-cells, encased in wooden boxes, were placed in a temperature-controlled room under constant lighting conditions and the temperature inside the TEM-cells was kept constant by circulating room air through the holes in the boxes. The rats were placed in plastic trays ( $14 \times 14 \times 7 \text{ cm}$ ) to avoid contact with the central plate and outer conductor. The bottom of the tray was covered with absorbing paper to collect excreta.

Ninety-six male and female Fischer 344 rats, weighing between 164–446 g (males:  $352 \pm 48 \text{ g}$ , females:  $206 \pm 17 \text{ g}$ ) were divided into 8 exposed groups (4 exposure levels, 2 different recovery times after exposure), each group consisting of 8 rats and 2 sham-exposed groups with 16 rats in each of the two groups. The peak power output (during the pulses) from the GSM mobile phone fed into two TEM-cells at a time were 1, 10, 100, and 1,000 mW per cell respectively, for a period of 2 h. This exposed the rats to peak power densities of 0.052, 0.52, 5.2, and  $52 \text{ W/m}^2$ , respectively. The average power and power-densities are 1/8 of the above values.

Theoretical FDTD-modeling of 2 rats placed in a TEM-cell (Martens et al., 1993) show that the maximum value of the electric field was 5% lower in the rat phantom placed in the lower compartment of the TEM-cell compared to its partner in the upper compartment. Also, the SAR-distribution was more uniform in the lower compartment, due to the larger distance to the septum (inner conductor) in the middle of the TEM-cell. These numerical simulations also showed that an input power of 1 W would result in a whole-body SAR-value of  $1.67 \text{ W/kg}$  in a small rat ( $< 250 \text{ g}$ ) placed in the upper compartment of the TEM-cell, while the lower compartment is kept empty.

When more than 1/3 of a TEM-cell compartment is occupied by the rat, or when both compartments are used simultaneously, the assumption that the animals do not perturb the electric field distribution in the cell significantly is no longer valid. Therefore, the average whole-body absorbed energy per rat was determined experimentally for rats of different weights placed in the upper, lower, or both compartments of a TEM-cell. For a constant input power, the power reflected at the entrance and the power transmitted through the TEM-cell were measured at least 5 times for each experimental condition. For each measurement, the orientation of the rat with respect to the propagation direction of the microwave radiation was noted, since whole-body SAR and brain SAR vary with orientation. For the actual

experimental situation with a rat in each compartment of the TEM-cell, the conversion factor  $K$  for SAR per unit of input power could be fitted to the data as:

$$K = (1.38 \pm 0.17) - (0.85 \pm 0.22) \cdot w \quad (1)$$

with  $w$  the sum of weights in kilograms of the 2 rats in the cell.

From Eq. (1), the SAR-values for the 4 exposure conditions can be determined to be 0.1, 1, 10, and 100 mW/kg for the male rats (350 g) and 0.13, 1.3, 13, and 130 mW/kg for the females (200 g).

In order to evaluate how orientation of the rat in the TEM-cell affects the SAR-values, brain SAR and whole-body SAR for 16 orientations of a 334 g rat phantom with respect to the incident radiation in the TEM-cell, were estimated in a FDTD-computation with the freely available FDTD program of Brooks Airforce Base (FDTD99) (LeBlanc et al., 2000). In a simplified geometry, the rat is exposed by a plane wave with a power density of 10 W/m<sup>2</sup> in a far-field condition. The average of SAR for the brain grey matter was 1.06 times the average whole-body SAR, with a standard deviation of 56% around the average value for the different orientations (Figure 1).

All animals were kept in the animal facilities for a recovery period of 14 or 28 dafter exposure. At the end of this period they were anaesthetized and sacrificed by perfusion-fixation with 4% formaldehyde. The brains were removed from the skull by non traumatic technique (resection of bone structures at the skull base, followed by a midline incision from the foramen magnum to the nose), after an extended *in situ* formalin perfusion *post mortem* fixation for 30 min. The brains were sectioned coronally (1–2 mm slices), embedded in paraffin and sliced at 5 µm, and were stained for RNA/DNA with cresyl violet which visualizes damaged neurons (“dark neurons”). Albumin antibodies (Dakopatts) were used to reveal albumin, seen as brownish spots or areas of more diffuse discolorations. The microscopical analysis

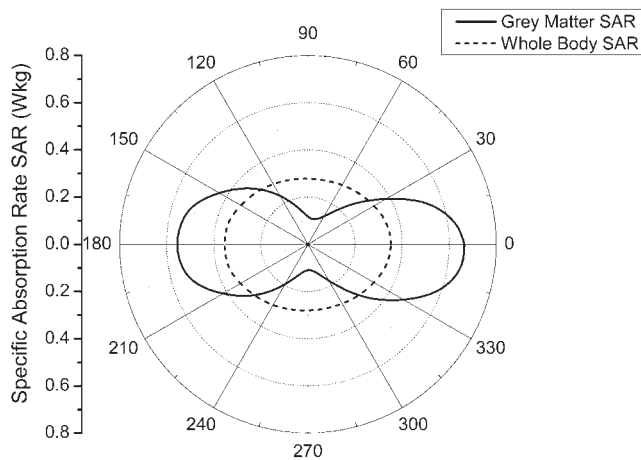


**Figure 1.** FDTD calculation of SAR-values in the brain grey matter and whole-body SAR (W/kg) in the rat at exposure to 900 MHz plane wave radiation, with a power density of 10 W/m<sup>2</sup>, as a function of incident wave angle with respect to the long axis of the animal. The polarization of the radiation is identical to the situation in the TEM-cell. An angle of 0° is defined as the head of the rat pointing in the direction of the plane wave.



**Figure 2.** Coronal section through frontal lobes with 8 foci of perivascular albumin leakage in frontal cortex and white matter, graded as 2.0 on a scale from (0–3). Immunostaining for albumin (SAR = 1.2 mW/kg).

was performed blind to the test situation by a neuropathologist, who judged and assigned the occurrence of albumin or “dark neurons” on a scale between 0 and 3 (for an example, see Figure 2).

As an initial discriminative test, the occurrence of an “effect” of exposure (score 1 or higher) was tested against sham-exposed (controls) using chi-squares analysis. The Kruskal Wallis one-way analysis of variance by ranks was used for a simultaneous statistical test of the score distributions for the 5 exposure conditions. When the null hypothesis could be rejected, comparisons between each of the exposure conditions and controls were made using the Mann-Whitney nonparametric test for independent samples.

The occurrence of covariates, such as gender and the position of the rat in the TEM-cell (upper/lower compartment), was evaluated using logistic regression.

## Results

In both test and control animals the normally occurring diffuse positive immunostaining for albumin in hypothalamus was found, serving as a built-in method control. In exposed animals, there were several albumin positive foci around capillaries in the white and grey matter (Figure 3). Here, the albumin had diffused into the neuropil between the cell bodies to surround neurons, which were either free of albumin or in some foci containing albumin (Figure 4). In addition, scattered neurons, not surrounded by albumin, were albumin positive.

Cresyl violet staining showed scattered and grouped dark neurons. These neurons were often shrunken and dark staining, homogenized with loss of discernible internal cell structures. Some of the dark neurons were also albumin positive or showed microvacuoles in the cytoplasm indicating an active pathological process. There was no evidence of haemorrhages or a glial reaction, astrocytic or microglial, adjacent to the changed neurons. Dark neurons were seen in all locations, intermingled with normal neurons especially in the cortex, hippocampus, and basal ganglia (Figures 5 and 6).



**Figure 3.** Three foci of albumin perivascular leakage in frontal white matter. Immunostaining for albumin (SAR = 1.2 mW/kg).

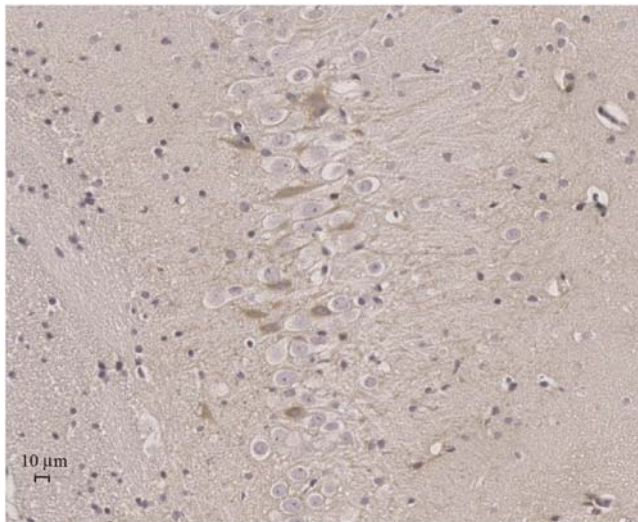


**Figure 4.** Hippocampal pyramidal cell row with albumin (brownish) uptake in some shrunken neurons (brownish) among preserved nerve cells. Albumin uptake in the surrounding neuropil including in axons and dendrites. Immunostaining for albumin (SAR = 1.2 mW/kg).

The occurrence of albumin outside brain vessels was characterized in three different ways: (i) albumin foci around vessels; (ii) diffuse occurrence of albumin in the brain; and (iii) albumin taken up in neurons. After 14 d recovery time, albumin foci were found significantly more often among exposed rats (29%) than among sham-exposed rats (0%) ( $p = 0.02$ ); see Table 1. Also after 14 d, uptake of albumin in neurons occurred more often in exposed animals (57%) than in sham-exposed (7%) ( $p = 0.001$ ). After 28 d of recovery, no significant difference in any of the albumin parameters was found between exposed and sham-exposed rats (Table 2), although

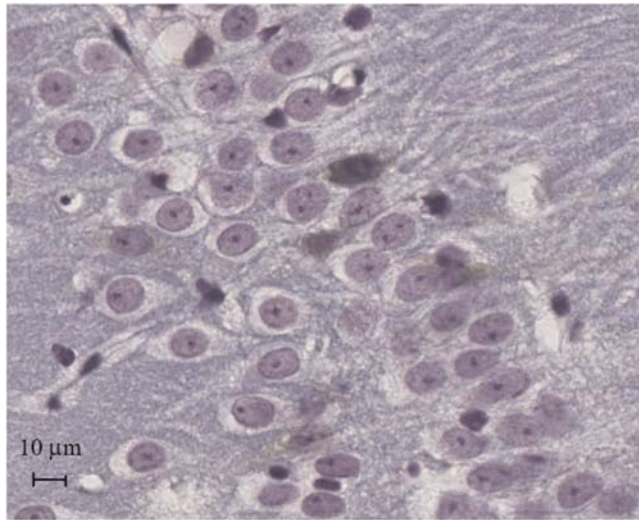


**Figure 5.** Albumin uptake in hippocampal neurons, some of them “dark” and slightly shrunk, among normal nerve cells. Immunostaining for albumin (SAR = 0.12 mW/kg).

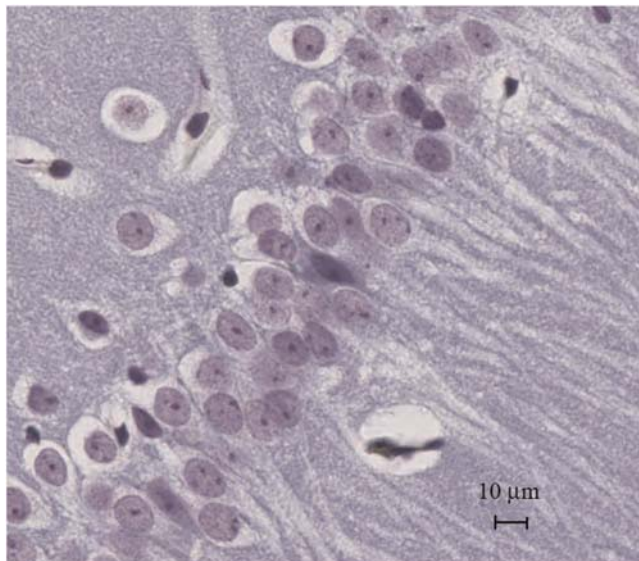


**Figure 6.** Dark neurons amongst preserved nerve cells in hippocampus. Cresyl violet (SAR = 0.12 mW/kg).

an increased occurrence of dark neurons was found in exposed rats (40%) as compared to sham exposed (13%) ( $p = 0.05$ , single sided test; Table 2).

Spearman’s nonparametric correlation analysis revealed a low but significant correlation between albumin uptake into neurons and the presence of dark neurons after 28 d ( $r_s = 0.41$ ,  $p = 0.01$ ), but not after 14 d. When taking into account the

**Table 1**

Crosstabulations (%) exposure versus biological parameter after 14 d recovery time

| Parameter                     |     | Exposure |               | <i>p</i> -Value (2-sided) |
|-------------------------------|-----|----------|---------------|---------------------------|
|                               |     | Exp.     | Sham controls |                           |
| Albumin foci (around vessels) | No  | 48       | 33            | 0.02                      |
|                               | Yes | 19       | 0             |                           |
| Diffuse albumin               | No  | 42       | 27            | 0.001                     |
|                               | Yes | 24       | 7             |                           |
| Neuronal albumin              | No  | 29       | 31            | 0.001                     |
|                               | Yes | 38       | 2             |                           |
| Dark neurons                  | No  | 42       | 22            |                           |
|                               | Yes | 25       | 11            |                           |

**Table 2**

Crosstabulations (%) exposed versus biological effect after 28 d recovery time

| Parameter                     |     | Exposure |               | <i>p</i> -Value (2-sided) |
|-------------------------------|-----|----------|---------------|---------------------------|
|                               |     | Exp.     | Sham controls |                           |
| Albumin foci (around vessels) | No  | 54       | 29            |                           |
|                               | Yes | 13       | 4             |                           |
| Diffuse albumin               | No  | 53       | 28            |                           |
|                               | Yes | 13       | 6             |                           |
| Neuronal albumin              | No  | 36       | 25            |                           |
|                               | Yes | 31       | 8             |                           |
| Dark neurons                  | No  | 39       | 31            | 0.05*                     |
|                               | Yes | 26       | 4             |                           |

\*1-Sided test.

level of exposure and quantification of the neuro-pathological effects investigated, it could be concluded, from a simultaneous nonparametric comparison of all 5 exposure levels (Kruskal Wallis test) that the distribution of albumin foci and neuronal albumin uptake differed significantly after 14 d, but not after 28 d following exposure (Figures 7–10). On the other hand, the distribution of dark neurons was found to differ only after 28 d ( $p = 0.01$ ) (Figures 11 and 12).

Pairwise comparisons between the different exposure levels and sham-exposed animals revealed statistically significant differences already at the lowest exposure levels (SAR = 0.12 mW/kg and 1.2 mW/kg) for all parameters but not for diffuse albumin occurrence (Figures 7, 9, and 12). Multivariate analysis did not reveal any influence of gender or the position of the animals in the TEM-cell (upper/lower compartment) on the frequency of occurrence of albumin parameters or dark neurons.

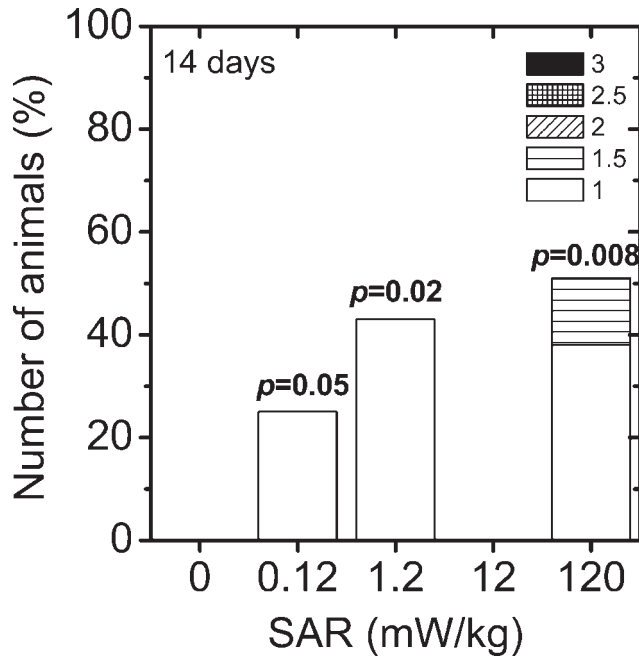


**Figure 7.** Percentage animals for varying SAR-values that are graded with values above 0.5 (on a scale from 0–3) for albumin foci around blood vessels in the brain after 14d recovery time following a single 2-h exposure to RF radiation from GSM-900 mobile phones ( $p$ -values relate to comparisons with the sham exposed controls). Kruskal Wallis statistic:  $p = 0.02$ .

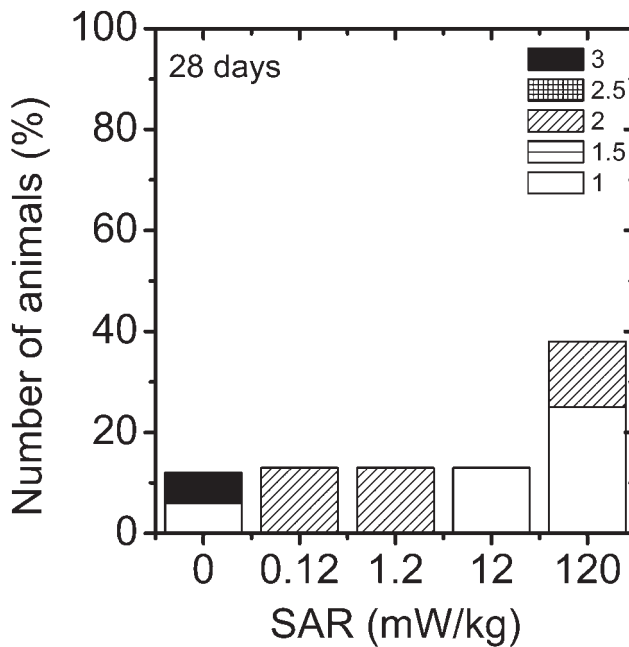


**Figure 8.** As in Figure 1, but after a recovery time of 28 d.

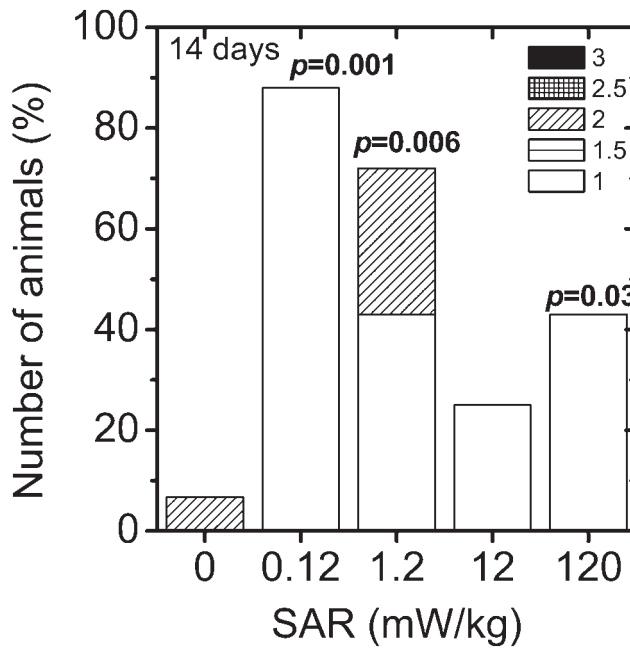


**Figure 9.** Percentage animals for varying SAR-values that are graded with values above 0.5 (on a scale from 0–3) for albumin uptake into neurons after 14 d recovery time following a single 2-h exposure to GSM-900 mobile phone radiation ( $p$ -values relate to comparisons with the sham exposed controls). Kruskal Wallis statistic:  $p = 0.002$ .

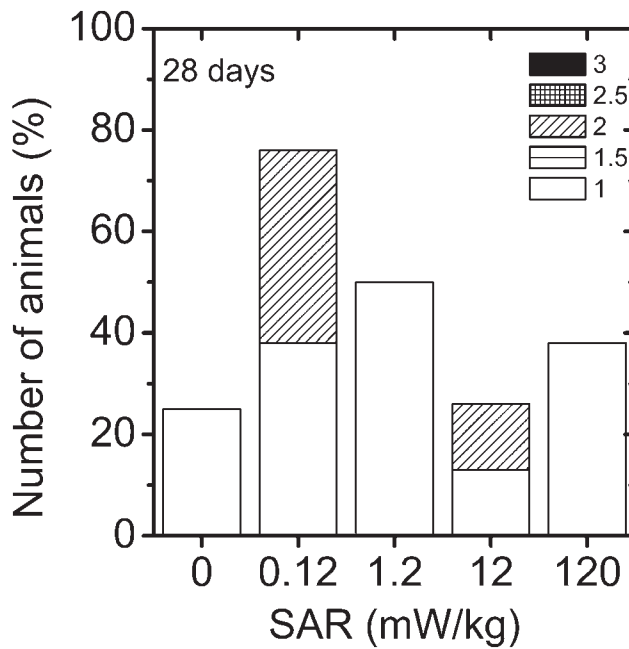


**Figure 10.** As in Figure 3, but after a recovery time of 28 d.

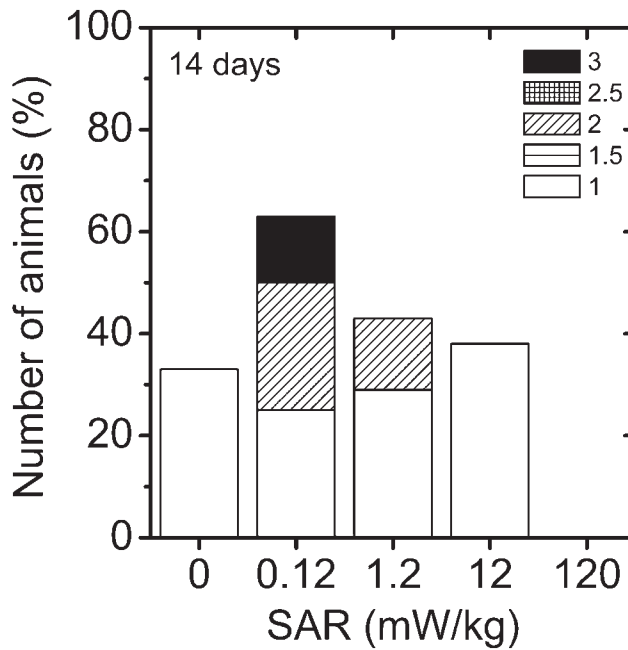


**Figure 11.** Percentage animals for varying SAR-values that are graded with values above 0.5 (on a scale from 0–3) for dark neurons after 14 d recovery time following a single 2-h exposure to GSM-900 mobile phone radiation.

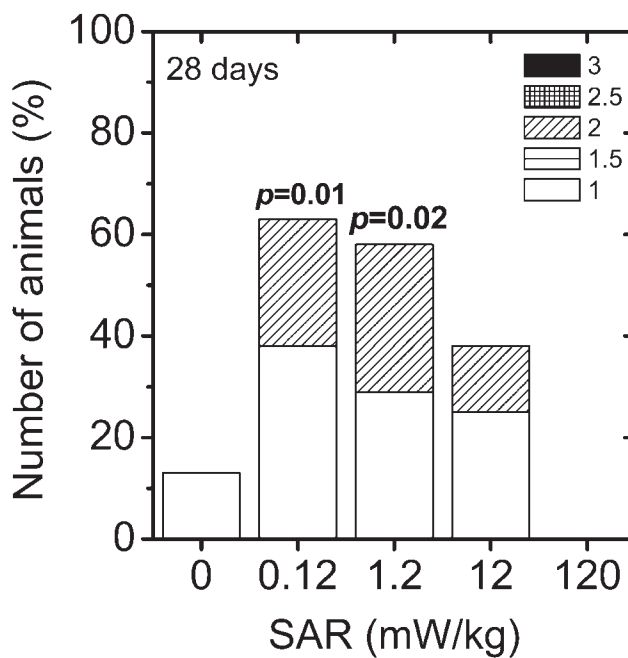


**Figure 12.** As in Figure 5, but after a recovery time of 28 d (*p*-values relate to comparisons with sham exposed controls). Kruskal Wallis statistic: *p* = 0.01.

## Discussion

A salient feature in the present study is that neuropathological changes occur already at SAR-values as low as 0.12 mW/kg. The results above are in agreement with the results of an earlier study (Persson et al., 1997). The SAR value of 0.12 mW/kg is far below the current recommended limit value for exposure to the head (2 W/kg) as used in the EU in accordance with the guidelines from ICNIRP (International Commission for Non-Ionizing Radiation). The recommendations of ICNIRP protect only against the heating of tissue by the radiation.

Especially striking is the amplitude windowing effect for albumin uptake into neurons with uptake in about 80% of the rats at SAR = 0.12 mW/kg. It should be pointed out that comparisons between our two control sub-groups did not reveal any statistical differences in the dark neuron and albumin parameters.

Oscar and Hawkins (1977) demonstrated that, at a frequency of 1,300 MHz, the BBB opened at extremely low SAR levels, even lower than those demonstrated by us (Figure 10). The frequency of occurrence of dark neurons was increased, as compared to sham-exposed animals both after 14 and 28 d of recovery, but reached statistical significance only 28 d after exposure.

The mechanism(s) responsible for opening of the BBB, albumin uptake in neurons or occurrence of neuronal damage, are not known today. Experiments on cultured endothelial cell layers could not reveal leakage caused by structural changes such as the opening of tight junctions (Leszczynski et al., 2002). However, these studies investigated passive transport associated effects and did not consider ATP facilitated active transport of substances through the endothelial cells. Most likely, the electromagnetic fields interact directly with biological molecules, activating pinocytosis and uptake of albumin in neurons. This is supported by studies carried out by Shivers et al. (1987).

The mechanisms leading to the observed neuronal damage can be direct or indirect. Direct in the sense that electromagnetic radiation causes cell death, for example by inducing apoptosis, and an indirect adverse effect due to toxic agents taken up into the neurons or released from stores in the neurons. These toxic agents can be albumin, or other substances conjugated to albumin and transported across the opened BBB after exposure to microwaves from GSM, or even substances released from the lysosomal vacuome. In the present study, a significant correlation was found between albumin uptake and occurrence of dark neurons 28 d, but not 14 d after exposure. This suggests a secondary, non reversible process taking place some weeks following the primary intoxication by substances crossing the BBB.

The question whether albumin leakage into the brain parenchyma constitutes a risk to the brain has been studied in a series of experimental situations. Neuronal degeneration has been observed in areas with BBB disruption: after intracarotid infusion of hyperosmolar solutions in rats (Salahuddin et al., 1988); in stroke-prone hypertensive rats (Fredriksson et al., 1988); and after acute hypertension by aortic compression in rats (Sokrab et al., 1988a,b).

Furthermore, epileptic seizures cause extravazation of plasma into brain parenchyma (Sokrab et al., 1990). The cerebellar Purkinje cells are heavily exposed to plasma constituents and degenerate in epileptic patients (Tunkel and Scheld, 1989). This effect may, however, be attributed to hypoxia as well.

It has been postulated that albumin is the most likely neurotoxin in serum (Eimerl and Schramm, 1991). Hassel et al. (1994) demonstrated that injection of

albumin into the brain parenchyma of rats gives rise to neuronal damage. When various amounts of albumin (25  $\mu$ l of either 3, 10 or 30 mg/ml rat albumin) was infused into rat neostriatum, neuronal cell death and severe axonal damage was seen in the cases of 10 and 30 mg/ml, but not for the 3 mg/ml solution. Also, as a secondary process, leakage of endogenous albumin in and around the area of neuronal damage is induced. An albumin dose of 10 mg/ml is approximately equivalent to 25% of the normal physiological serum concentration.

It is still unclear whether the albumin leakage demonstrated in our experiments reaches concentrations that damage neurons but the fact that this study shows a significant correlation between albumin uptake and occurrence of dark neurons 28 d after exposure, might indicate that a relation exists.

The dose-response relationship for dark neurons in this study differs from our earlier results on effects after a 50-d recovery period following one single exposure (Salford et al., 2003). In that study, the frequency of occurrence of dark neurons was highest at SAR = 200 mW/kg (the corrected value according to the recent measurements is 120 mW/kg). The reason for this difference is unknown, but it could be hypothesized that different damaging mechanisms operate at different time.

A recent study by Poullétier de Gannes et al. (2006) failed to detect BBB leakage or occurrence of dark neurons 14 or 50 d after a 2-h exposure to GSM-900 radiation at average brain SAR values of 0.14 and 2.0 W/kg. Only long-term animal studies can answer the question whether irreversible adverse effects can be caused by radiation from mobile phones and at what energy levels (one such study where rats are exposed to GSM radiation once a week for 13 months is under way in our laboratory). The most remarkable observation in our studies on the effects of microwaves on the BBB is the fact that the lower SAR values (around 1 mW/kg) give rise to a more pronounced albumin leakage than the higher SAR values. If increase in dose had led to increased response, we feel that the risk of cellular telephones, base-stations, and other RF-emitting sources could be managed by reduction of their emitted energy. The indications from our study that the weakest fields are the biologically most harmful, poses a complicated problem. The most pronounced BBB-opening effect of the mobile telephone may not be in the most superficial layers of the brain, but several centimetres deep in central cerebral structures.

It seems quite possible that bystanders in the vicinity of mobile phone users may be affected through a passive GSM exposure, as well as larger groups exposed from distant base-stations. More, substantial research is needed, however, before reliable dose-response relationships can be established that can form the basis for recommendations for future exposure limit values that take into account non thermal effects of microwaves from mobile communications on the human brain.

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