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Nerve Cell Damage in Mammalian Brain after Exposure to Microwaves from GSM Mobile Phones

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The possible risks of radio-frequency electromagnetic fields for the human body is a growing concern for our society. We have previously shown that weak pulsed microwaves give rise to a significant leakage of albumin through the blood–brain barrier. In this study we investigated whether a pathologic leakage across the blood–brain barrier might be combined with damage to the neurons. Three groups each of eight rats were exposed for 2 hr to Global System for Mobile Communications (GSM) mobile phone electromagnetic fields of different strengths. We found highly significant ($p < 0.002$) evidence for neuronal damage in the cortex, hippocampus, and basal ganglia in the brains of exposed rats. *Key words:* **blood–brain barrier, central nervous system, microwaves, mobile phones, neuronal damage, rats.** *Environ Health Perspect* **111:881–883 (2003). doi:10.1289/ehp.6039 available via *http://dx.doi.org/* [Online 29 January 2003]**

The voluntary exposure of the brain to microwaves from hand-held mobile phones by one-fourth of the world's population has been called the largest human biologic experiment ever (Salford et al. 2001). In the near future, microwaves will also be emitted by an abundance of other appliances in the cordless office and also in the home. The possible risks of radio-frequency electromagnetic fields (RF EMFs) for the human body is a growing concern for our society (for a review, see Hyland 2000). Most researchers in the field have dwelled on the question of whether RF EMFs may induce or promote cancer growth. Although some have indicated increased risk (Hardell et al. 2002; Repacholi et al. 1997), most studies, including our own, have shown no effects (Salford et al. 1997a) or even a decreased risk (Adey et al. 1999).

The possible risks of microwaves for the human body has attracted interest since the 1960s (i.e., before the advent of mobile phones), when radar and microwave ovens posed a possible health problem. Oscar and Hawkins (1977) performed early studies on effects of RF EMFs on the blood–brain barrier. They demonstrated that at very low energy levels (< 10 W/m^2), the fields in a restricted exposure window caused a significant leakage of ^{14}C-mannitol, inulin, and also dextran (same molecular weight as albumin) from the capillaries into the surrounding cerebellar brain tissue. These findings, however, were not repeated in a study using ^{14}C-sucrose (Gruenau et al. 1982). A recent *in vitro* study has shown that EMF at 1.8 GHz increase the permeability of the blood–brain barrier to sucrose (Schirmacher et al. 2000). Shivers and colleagues (Shivers et al. 1987; Prato et al. 1990) examined the effect of magnetic resonance imaging upon the rat brain. They showed that the combined exposure to RF EMFs and pulsed and static magnetic fields gave rise to a significant pinocytotic transport of albumin from the capillaries into the brain.

Inspired by this work, since 1988 our group has studied the effects of different intensities and modulations of 915 MHz RF EMFs in a rat model where the exposure takes place in a transverse electromagnetic transmission line chamber (TEM-cell) during various time periods. In series of more than 1,600 animals, we have proven that subthermal power densities from both pulse-modulated and continuous RF EMFs—including those from GSM (Global System for Mobile Communications) mobile phones—have the potency to significantly open the blood–brain barrier such that the animals' own albumin (but not fibrinogen) passes out of the bloodstream into the brain tissue and accumulates in the neurons and glial cells surrounding the capillaries (Malmgren 1998; Persson et al. 1997; Persson and Salford 1996; Salford et al. 1992, 1993, 1994, 1997b, 2001) (Figure 1). These results have been duplicated recently in another laboratory (Töre et al. 2001). Similar results have been reported by others (Fritze et al. 1997).

We and others (Oscar and Hawkins 1977; Persson et al. 1997) have pointed out that when such a relatively large molecule as albumin can pass the blood–brain barrier, so too can many other smaller molecules, including toxic ones, which may escape into the brain because of exposure to RF EMFs. We have hitherto not concluded that such leakage is harmful for the brain. However, Hassel et al. (1994) have shown that autologous albumin injected into the brain tissue of rats leads to damage to neurons at the injection site when the concentration of albumin in the injected solution is at least 25% of that in blood. In the present study, we investigated whether leakage across the blood–brain barrier might cause damage to the neurons.

Materials and Methods

TEM-cells used for the RF EMF exposure of rats were 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 was connected via a coaxial cable to the TEM-cell; no voice modulation was applied.

The TEM-cell is enclosed in a wooden box (15 × 15 × 15 cm) 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 aluminum.

The TEM-cells were placed in a temperature-controlled room, and the temperature in the TEM-cells was kept constant by circulating room air through holes in the wooden box.

The specific absorption rate (SAR) distribution in the rat brain has been simulated with the finite-difference time-domain method (Martens et al. 1993) and found to vary < 6 dB in the rat brain.

The rats were placed in plastic trays (12 × 12 × 7 cm) to avoid contact with the central plate and outer conductor. The bottom of the tray was covered with absorbing paper to collect urine and feces.

Thirty-two male and female Fischer 344 rats 12–26 weeks of age and weighing 282 ± 91 g were divided into four groups of eight rats each. The peak output power of 10 mW, 100 mW, and 1,000 mW per cell from the GSM mobile telephone was fed into two TEM-cells simultaneously for 2 hr. This exposed the rats to peak power densities of 0.24. 2.4, and 24 W/m^2, respectively. This exposure resulted in average whole-body SARs of 2 mW/kg, 20 mW/kg, and 200 mW/kg, respectively. For further details about exposure conditions and SAR calculations, see Martens et al. (1993) and Malmgren (1998). The fourth group of rats was simultaneously

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kept for 2 hr in nonactivated TEM-cells. The animals were awake during the exposure and could move and turn within the exposure chamber.

The animals in each exposure group were allowed to survive for about 50 days after exposure. They were carefully observed daily for neurologic and behavioral abnormalities during this period, at the end of which they were anesthetized and sacrificed by perfusion fixation with 4% formaldehyde.

The brains were removed from the skull by nontraumatic 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* postmortem fixation time of 30 min. Each brain was sectioned coronally in 1–2-mm-thick slices, which all were embedded in paraffin, cut in 5-µm sections, and stained for RNA/DNA with cresyl violet to show dark neurons. Applying albumin antibodies (Dakocytomation Norden AB, Älvsjö, Sweden) reveals albumin as brownish spotty or more diffuse discolorations (Salford et al. 1994).

The occurrence of "dark neurons" was judged semiquantitatively by the neuropathologist as 0 (no or occasional dark neurons), 1 (moderate occurrence of dark neurons), or 2 (abundant occurrence). The microscopic analysis was performed blind to the test situation. The Kruskal-Wallis one-way analysis of variance by ranks was used for a simultaneous statistical test of the score distributions for the four exposure conditions. When the null hypothesis could be rejected, comparisons between controls and each of the exposure conditions was made with the Mann-Whitney nonparametric test for independent samples.

Results and Discussion

Controls and test animals alike showed the normal diffuse positive immunostaining for albumin in hypothalamus, a kind of built-in method control.

Control animals showed either no positivity or an occasional and often questionable positivity for albumin outside the hypothalamus (Figure 1A). In one control animal we observed a moderate number of dark neurons, but no such change was observed in all the other controls.

Exposed animals usually showed several albumin-positive foci around the finer blood vessels in white and gray matter (Figure 1B). Here the albumin had spread in the tissue between the cell bodies and surrounded neurons, which either contained no albumin or contained albumin in some foci. Scattered neurons, not associated with albumin leakage between the neurons, were also positive.

The cresyl violet staining revealed scattered and grouped dark neurons, which were often shrunken and darkly stained, homogenized with loss of discernible internal cell structures. Some of these dark neurons were also albumin positive or showed cytoplasmic microvacuoles indicating an active pathologic process. There were no hemorrhages and no discernible glial reaction, astrocytic or microglial, adjacent to changed neurons. Changed neurons were seen in all locations, but especially the cortex, hippocampus, and basal ganglia, mixed in among normal neurons (Figure 2). The percentage abnormal neurons is roughly appreciated to be maximally around 2%, but in some restricted areas they dominated the picture.

The occurrence of dark neurons under the different exposure conditions is presented in Figure 3, which shows a significant positive relation between EMF dosage (SAR) and number of dark neurons.

A combined nonparametric test for the four exposure situations simultaneously revealed that the distributions of scores differed significantly between the groups ($p < 0.002$).

We present here for the first time evidence for neuronal damage caused by nonthermal microwave exposure. The cortex as well as the hippocampus and the basal ganglia in the brains of exposed rats contained damaged neurons. We realize that our study comprises few animals, but the combined results are highly significant and exhibit a clear dose–response relation.

We considered the observed dark neurons not to be artifacts for the following reasons: first, the brains were removed atraumatically and perfusion fixed *in situ*; second, the dark

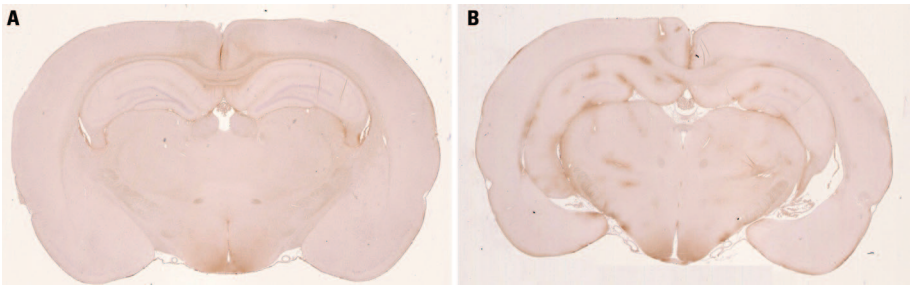


Figure 1. Cross-section of central parts of the brain of (*A*) an unexposed control rat and (*B*) an RF EMF-exposed rat, both stained for albumin, which appears brown. In (*A*), albumin is visible in the central inferior parts of the brain (the hypothalamus), which is a normal feature. In (*B*), albumin is visible in multiple small foci representing leakage from many vessels. Magnification, about ×3.

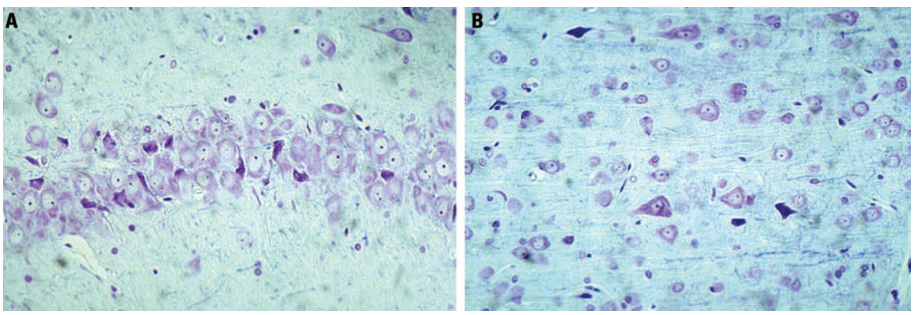


Figure 2. Photomicrograph of sections of brain from an RF EMF-exposed rat stained with cresyl violet. (*A*) Row of nerve cells in a section of the pyramidal cell band of the hippocampus; among the normal nerve cells (large cells) are interspersed black and shrunken nerve cells, so-called dark neurons. (*B*) The cortex, top left, of an RF EMF-exposed rat showing normal nerve cells (pale blue) intermingled with abnormal, black and shrunken "dark neurons" at all depths of the cortex, but least in the superficial upper layers. Magnification, ×160.

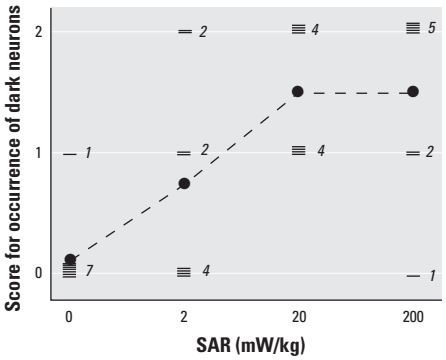


Figure 3. Distribution of scores for the occurrence of "dark neurons" as a function of exposure condition. The dashed line connects mean values for each condition. Numbers in the figure indicate the number of animals in the treatment group with that score. A simultaneous nonparametric comparison of all four conditions revealed significant differences ($p < 0.002$). As compared to control, $p < 0.2$ for 2 mW/kg; $p = 0.01$ for 20 mW/kg; and $p = 0.03$ for 200 mW/kg.

neurons were intermingled with normal-appearing neurons (see Figure 2). Also, the presence of vacuoles in several of the dark neurons is a clear sign that damage occurred in the living animal. We cannot exclude that the neuronal change described may represent apoptotic cell death.

The neuronal albumin uptake and other changes described would seem to indicate serious neuronal damage, which may be mediated through organelle damage with release of not only hydrolytic lysosomal enzymes but also, for example, sequestered harmful material, such as heavy metals, stored away in cytoplasmic organelles (lysosomes).

The time between last exposure and sacrifice is of great importance for the detection of foci of leakage because extravasated albumin rapidly diffuses down to, and beyond, concentrations possible to demonstrate accurately immunohistologically. However, the initial albumin leakage into the brain tissue (seen within hours in ~40% of exposed animals in our previous studies) may start a secondary blood–brain barrier opening, leading to a vicious circle—because we demonstrate albumin leakage even 8 weeks after the exposure.

We chose 12–26-week-old rats because they are comparable with human teenagers—notably frequent users of mobile phones—with respect to age. The situation of the growing brain might deserve special concern from society because biologic and maturational processes are particularly vulnerable during the growth process. The intense use of mobile phones by youngsters is a serious consideration. A neuronal damage of the kind described here may not have immediately demonstrable consequences, even if repeated. In the long run, however, it may result in reduced brain reserve capacity that might be unveiled by other later neuronal disease or even the wear and tear of aging. We cannot exclude that after some decades of (often) daily use, a whole generation of users may suffer negative effects, perhaps as early as in middle age.

Correction

Figure 1 in the original manuscript was cited in "Materials and Methods" and illustrated albumin leakage that we had reported earlier. The figure showed examples of cross-sections of the brains of rats sacrificed immediately after exposure to microwaves. Because this could be misunderstood, in the interest of clarity and with the permission of the editor, we have replaced that figure.

The new Figure 1 is now cited in "Results" and shows animals from the present study. Figure 1A illustrates the brain of a sham-exposed control animal, and Figure 1B illustrates an animal exposed to 2 mW/kg for 2 hr.

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