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NON-THERMAL EFFECTS AND MECHANISMS OF INTERACTION BETWEEN ELECTROMAGNETIC FIELDS AND LIVING MATTER

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CONTENTS

Dependence of non-thermal biological effects of microwaves on physical and biological variables: implications for reproducibility and safety standards

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Abstract

Diverse biological responses, including adverse health effects, to non-thermal (NT) microwaves (MW) have been described by many research groups all over the world. The aim of this paper is to provide an overview of the complex dependence of these effects on various physical and biological parameters, which must be controlled in replication studies.
Besides well-known dependencies on carrier frequency and modulation, emerging data suggest dependencies of NT MW effects on polarization, intermittence and coherence time of exposure, static magnetic field, electromagnetic stray fields, genotype, gender, physiological and individual traits, cell density during exposure. Data also indicate that duration of exposure may be as important as power density (PD) and specific absorption rate (SAR). Further evaluation of these dependencies are needed for understanding the mechanisms by which NT MW affect biological systems, planning *in vivo* and epidemiological studies, developing medical treatments, setting safety standards, and minimizing the adverse effects of MW from mobile communication.

***Key words*: non-thermal effects of microwaves, mobile (cellular) phones, safety standards.**

List of abbreviations:
Anomalous viscosity time dependence (AVTD); blood-brain barrier (BBB); catalase (CAT); Digital Enhanced (former European) Cordless Telecommunications (DECT); circularly polarized (CP); continuous wave (CW); Digital Advanced Mobile Phone System (DAMPS); discontinuous transmission (DTX); electroencephalographic (EEG); electromagnetic field (EMF); embryonic stem (ES) cells; ethidium bromide (EtBr); extremely low frequency (ELF); Gaussian Minimum Shift Keying (GMSK); Ginkgo biloba (Gb); Global System for Mobile Communication (GSM); glutathione peroxidase (GSH-Px); International Commission for Non-Ionizing Radiation Protection (ICNIRP); linearly polarized (LP); malondialdehyde (MDA); micronucleus (MN) assay; microwaves (MWs); N-acetyl-beta-d-glucosaminidase (NAG); nitric oxide (NO); non-thermal (NT); ornithine decarboxylase (ODC); phorbol ester 12-myristate 13-acetate (PMA); phosphorylated H2AX histone (γ-H2AX); power density (PD);

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regional cerebral blood flow (rCBF); Russian National Committee on Non-Ionizing Radiation Protection (RNCNIRP); specific absorption rate (SAR); static magnetic field (SMF); superoxide dismutase (SOD); Time Division Multiple Access (TDMA); tumor suppressor p53 binding protein 1 (53BP1); ultraviolet (UV); Universal Mobile Telecommunications System (UMTS).

Introduction

Exposures to non-ionizing electromagnetic fields vary in many parameters: power (specific absorption rate, incident power density), wavelength/frequency, near field/far field, polarization (linear, circular), continues wave (CW) and pulsed fields (that include variables such as pulse repetition rate, pulse width or duty cycle, pulse shape, pulse to average power, etc.), modulation (amplitude, frequency, phase, complex), static magnetic field (SMF) and electromagnetic stray fields at the place of exposure, overall duration and intermittence of exposure (continuous, interrupted), acute and chronic exposures. With increased absorption of energy, so-called thermal effects of microwaves (MW) are usually observed that deal with MW-induced heating. Specific absorption rate (SAR) or power density (PD) is a main determinate for thermal MW effects. Several other physical parameters of exposure have been reported to be of importance for so-called non-thermal (NT) biological effects, which are induced by MW at intensities well below any measureable heating[1-11]. An important question is how these physical parameters could be taken into account in setting safety standards.

Most often, current safety standards are based on thermal MW effects observed in short-term (acute) exposures. On the other hand, NT MW effects, especially those induced during prolonged (chronic) exposures, are accepted and taken into account for setting the national safety standards in some countries such as Russia[10-12]. It should be noted that, in contrast to the ICNIRP (International Commission for Non-Ionizing Radiation Protection) safety standards[13] which are based on the acute thermal effects of MW, the standards adopted by the Russian National Committee on Non-Ionizing Radiation Protection (RNCNIRP) are based on experimental data from chronic (up to 4 month) exposures of animals to MW at various physical parameters including intensity, frequency and modulation, obtained from research performed in the former Soviet Union[10-12].

Since setting the current safety standards, the situation with exposure of the general population to MW has changed significantly. Nowadays, most of the human population is chronically exposed to MW signals from various sources including mobile phones and base stations. These exposures are characterized by low intensities, varieties and complexities of signals, and long-term durations of exposure that are comparable with a lifespan. So far, the “dose” (accumulated absorbed energy that is measured in radiobiology as the dose rate multiplied by exposure time) is not adopted for the MW exposures and SAR or PD is usually used for guidelines. To what degree SAR/PD can be applied to the nowadays NT MW chronic exposures is not known and the current state of research demands reevaluation of the safety standards[12].

There are two main approaches to treat numerous data regarding NT MW effects. The first one is based on the consideration of these effects in dependence on various physical parameters and biological variables as has consistently been described in many experimental studies and will be reviewed in this paper. The second approach is based on neglecting or minimizing the experimentally observed NT MW effects based on the current state of theoretical physical science that is insufficient for comprehensive expla-

nation of the NT MW effects. As a result of such various treatments of the experimental data, the safety standards significantly vary, up to 1000 times, among countries.

The literature on the NT MW effects is very broad. There are four lines of evidence for the NT MW effects: (1) altered cellular responses in laboratory *in vitro* studies and results of chronic exposures *in vivo* studies[3, 11, 14]; (2) results of medical application of NT MW in the former Soviet Union countries[4, 7, 15, 16]; (3) hypersensitivity to electromagnetic fields (EMF); (4) epidemiological studies suggesting increased cancer risks for mobile phone users[17-19].

This paper is not intended to be a comprehensive review of this literature. In this review, we will focus on the studies which evaluate dependence of the NT MW effects on physical parameters and biological variables.

Experimental studies

The first data on the NT effects of MW in so-called millimeter range (wavelength 1-10 mm in vacuum) was obtained by Vilenskaya and co-authors[20] and Devyatkov[21]. Highly resonant effects of ultra-weak MW (near 70 GHz) on the induction of λ-phage were first established by Webb[22], and subsequently corroborated[23]. In these and subsequent studies the observed spectra of MW action were found to have the following common properties: (1) the MW effects were strongly dependent on the frequency (frequency windows), (2) there was an associated power (intensity) threshold below which no effect was observed, and above which the effects of exposure depended only weakly on power over several orders of magnitude (so-called S-shaped or sigmoid dependence), (3) the occurrence of MW effects depended on the duration of exposure, a certain minimum duration of exposure was necessary for an effect to manifest itself. These important regularities of the NT MW effects have previously been reviewed[2, 7-9, 24-27].

The first investigations of the NT MW effects at lower frequency ranges were performed by Blackman and colleagues[28-30] and Adey and colleagues[31, 32]. These groups found dependence of the NT MW effects on modulation.

Since that time, other groups have confirmed and extended the main findings of these pioneering studies as will be reviewed below.

Frequency dependence and frequency windows

The effects of NT MW on DNA repair in *E. coli* K12 AB1157 were studied by the method of anomalous viscosity time dependence (AVTD)[33, 34]. The AVTD method is a sensitive technique to detect changes in conformation of nucleoids/chromatin induced by either genotoxic or stress factors[35-40]. Significant inhibition of DNA repair was found when X-ray-irradiated cells were exposed to MW within the frequency ranges of 51.62-51.84 GHz and 41.25-41.50 GHz. The effects were observed within two "frequency windows", both displaying a pronounced resonance character with the resonance frequencies of 51.755 GHz and 41.32 GHz, respectively[33, 34]. Of note, these MW effects were observed at PD well below any thermal effects and could not be accounted for by heating. The frequency windows of resonance type have often been termed "resonances" as also will be used below.

The resonance frequency of 51.755 GHz was stable within the error of measurements, ±1 MHz with decreasing the PD from $3 \cdot 10^{-3}$ to 10^{-19} W/cm^2 [34, 35]. At the same time, the

half-width of the resonance decreased from 100 MHz to 3 MHz revealing an extremely sharp dependence on frequency ($Q \sim 10^4$). This sharp narrowing of the 51.755 GHz resonance with decreasing the PD from $3 \cdot 10^{-3}$ to 10^{-7} W/cm^2 followed by an emergence of new resonances, 51.675±0.001, 51.805±0.002, and 51.835±0.005 GHz[35, 41]. The half-widths of all these resonances including the main one, 51.755±0.001 GHz, were about 10 MHz at the PD of 10^{-10} W/cm^2. These data were interpreted in the framework of the model of electron-conformational interactions as a splitting of the main resonance 51.755 GHz by the MW field[35].

The MW effects were studied at different PD and several frequencies around the resonance frequency of 51.675 GHz[41]. This resonance frequency was found to be stable, ± 1 MHz, within the PD range of 10^{-18} - 10^{-8} W/cm^2. Along with disappearance of the 51.675 GHz resonance response at the sub-thermal PD of 10^{-6} - 10^{-3} W/cm^2, a new resonance effect arose at 51.688±0.002 GHz[41]. This resonance frequency was also stable within the PD range studied.

Taken together, these data[34, 35, 41] suggested a sharp rearrangement of the frequency spectra of MW action, which was induced by the sub-thermal MW. The half-widths of all three resonances depended on PD, changing either from 2-3 MHz to 16-17 MHz (51.675 GHz and 51.668 GHz resonances) or from 2-3 MHz to 100 MHz (51.755 GHz resonance)[35, 41]. The data indicated also that dependencies of half-width on PD might vary for different resonance frequencies.

Significant narrowing in resonance response with decreasing PD has been found when studying the growth rate in yeast cells[42] and chromatin conformation in thymocytes of rats[43]. In the Gründler's study, the half-width of the resonance (near 41 GHz) decreased from 16 MHz to 4 MHz as PD decreased from 10^{-2} W/cm^2 to 5 pW/cm^2[42].

Thus, the results of studies with different cell types indicate that narrowing of the resonance window upon decrease in PD is one of the general regularities in cell response to NT MW. This regularity suggests that many coupled oscillators are involved non-linearly in the response of living cells to NT MW as has previously been predicted by Fröhlich[44].

Gapeev *et al.* studied effects of MW exposure (frequency range 41.75-42.1 GHz, frequency increment 50 MHz, PD 240 μW/cm^2) on the respiratory burst induced by calcium ionophore A23187 and phorbol ester 12-myristate 13-acetate (PMA) in the peritoneal neutrophils of mice[45, 46]. MW inhibited the respiratory burst. MW effect displayed resonance-like dependence on frequency, the resonance frequency and half-width of the resonance being 41.95 GHz and 160 MHz, respectively ($Q = 260$)[45, 46]. In other studies, Gapeev *et al.* analyzed acute zymosan-induced paw edema in mice[47, 48]. MW exposure of animals at the PD of 0.1 mW/cm^2 resulted in decrease of the paw edema that was frequency-dependent in the range of 42-43 GHz.

Based on the extrapolation from the data obtained in the extremely high frequency range (30-300 GHz), the values for half-width of resonances at the frequency range of mobile phones (0.9–2 GHz) were estimated to be 1-10 MHz[40]. Effects of GSM (Global System for Mobile Communication) MW on chromatin conformation and 53BP1 (tumor suppressor p53 binding protein 1)/γ-H2AX (phosphorylated H2AX histone) DNA repair foci in human lymphocytes were studied in this frequency range[38-40, 49]. Dependence of these MW effects on carrier frequency was observed[38, 40, 49]. This dependence was replicated in independent experiments with lymphocytes from twenty six healthy and hypersensitive persons[38, 39, 49].

Tkalec and colleagues exposed duckweed (*Lemna minor L.*) to MW at the frequencies of 400, 900, and 1900 MHz[50]. The growth of plants exposed for 2 h to a 23 V/m

electric field of 900 MHz significantly decreased in comparison with the control, while an electric field of the same strength but at 400 MHz did not have such effect. A modulated field at 900 MHz strongly inhibited the growth, while at 400 MHz modulation did not influence the growth significantly. At both frequencies, a longer exposure mostly decreased the growth and the highest electric field (390 V/m) strongly inhibited the growth. Exposure of plants to lower field strength (10 V/m) for 14 h caused a significant decrease at 400 and 1900 MHz while 900 MHz did not influence the growth. Peroxidase activity in exposed plants varied, depending on the exposure characteristics. Observed changes were mostly small, except in plants exposed for 2 h to 41 V/m at 900 MHz where a significant increase (41%) was found. The authors concluded that MW might influence plant growth and, to some extent, peroxidase activity. However, the effects of MW strongly depended on the characteristics of the field exposure such as frequency and modulation. These dependences were confirmed in further study of the same group[51, 52].

Remondini *et al.* analyzed changes in gene expression in human EA.hy926 endothelial cells using gene microarrays[53]. Cells were exposed to MW (SAR 1.8-2.5 W/kg, 1 h exposure) either at 900-MHz GSM Basic mode or 1800-MHz GSM Basic mode. Exposure to 900 MHz resulted in up-regulation in 22 genes and down-regulation in 10 genes. No significant change in gene expression was observed after exposure to 1800 MHz.

Sigmoid intensity dependences and power windows

It was found by Devyatkov et al. that NT MW effects display sigmoid dependence on intensity above certain intensity thresholds[21]. This type of PD dependence for the MW effects was observed in other studies as previously reviewed[7-9, 24, 25].

The data obtained in experiments with *E coli* cells and rat thymocytes provided new evidence for sigmoid type of PD dependence and suggested that similar to ELF effects, MW effects may be observed within specific "intensity windows"[35, 41, 43, 54]. The most striking example of the sigmoid PD dependence was found at the resonance frequency of 51.755 GHz[35]. When exposing *E. coli* cells at the cell density of $4 \cdot 10^8$ cell/ml, the effect reached saturation at the PD of 10^{-18}-10^{-17} W/cm^2 and did not change up to PD of 10^{-3} W/cm^2. In these experiments, the direct measurements of PD below 10^{-7} W/cm^2 were not available and lower PD was obtained using calibrated attenuators. Therefore, some uncertainty in the evaluation of the lowest PD was possible. The background MW radiation in this frequency range has been estimated to be 10^{-21}-10^{-19} W/m^2/Hz[55]. Based on the experimentally determined half-width of the 51.755 GHz resonance, 1 MHz[35], the background PD was estimated as 10^{-19}-10^{-17} W/cm^2 within the 51.755 GHz resonance. The resonance MW effects on *E. coli* cells were observed at the PD very close to the estimated background value[35, 41, 56-58]. These data suggested that the PD dependence of MW effect at the specific resonance frequencies might have a threshold comparable with the background level. Dependence of the MW effect on PD at one of the resonance frequencies, 51.675 GHz, had the shape of "intensity window" in the PD range from 10^{-18} to 10^{-8} W/cm^2 [41]. It is interesting, that no MW effect at this resonance frequency was observed at sub-thermal and thermal PD. This type of PD dependence has supported hypothesis about possible rearrangement of the frequency MW spectra action by the MW field[35]. The position of the PD window varied between different resonance frequen-

cies and depended on cell density during exposure of cells[41]. Despite some uncertainty in the evaluation of PD at the levels below 10^{-7} W/cm^2 in the referred studies the data indicated that NT MW at the resonance frequencies may result in biological effects at very low intensities comparable with intensities from base stations and other MW sources used in mobile communication.

Gapeev *et al.* have studied dependence of the MW effects at the resonance frequency of 41.95 GHz on the respiratory burst induced by calcium ionophore A23187 and PMA in the peritoneal neutrophils of mice[45, 46]. Inhibitory effects of MW exposure has been observed at the PD of 0.001 mW/cm^2 and displayed sigmoid dependence on PD at higher power densities[45, 46].

In other study, Gapeev *et al.* analyzed acute zymosan-induced paw edema in mice[48]. MW exposure of animals at the frequency of 42.2GHz and exposure duration of 20 min decreased the paw edema. Sigmoid dependence of this effect on PD has been obtained with a maximum reached at the PD of 0.1 mW/cm^2.

In their pioneering study on blood-brain barrier (BBB) permeability, Oscar and Hawkins exposed rats to MW at 1.3 GHz and analyzed BBB permeability by measuring uptake of several neutral polar substances in certain areas of the brain[59]. A single, 20 min exposure, to continuous wave (CW) MW increased the uptake of D-mannitol at average power densities of less than 3 mW/cm^2. Increased permeability was observed both immediately and 4 h after exposure, but not 24 h after exposure. After an initial rise at 0.01 mW/cm^2, the permeability of cerebral vessels to saccharides decreased with increasing microwave power at 1 mW/cm^2. Thus, the effects of MW were observed within the power window of 0.01-0.4 mW/cm^2. Differences in the level of uptake occurred between effects of CW MW and pulsed MW of the same average power. Microwaves of the same average power but different pulse characteristics also produced different uptake levels.

These findings on "power windows" for BBB permeability have been subsequently corroborated by the group of Persson and Salford[60, 61]. In their recent study, the effects of GSM MW on the permeability of the BBB and signs of neuronal damage in rats were investigated using a real GSM programmable mobile phone in the 900 MHz band[62]. The rats were exposed for 2 h at an SAR of 0.12, 1.2, 12, or 120 mW/kg. Albumin extravasation and also its uptake into neurons increased after 14 d. The occurrence of dark neurons in the rat brains increased later, after 28 d. Both effects were seen already at 0.12 mW/kg with only slight increase, if any, at higher SAR values.

Duration of exposure and time after exposure

Bozhanova with co-authors reported that the effect of cellular synchronization induced by NT MW depended on duration of exposure and PD[63]. The dependence on duration of exposure fitted to exponential function. The important observation was that in order to achieve the same synchronization of cells, the decrease in PD could be compensated by the increase in the duration of exposure.

Kwee and Raskmark analyzed effects of MW at 960 MHz and various SARs, 0.021, 0.21, and 2.1 mW/kg on proliferation of human epithelial amnion cells[64]. These authors reported linear correlations between exposure time to MW at 0.021 and 2.1 mW/kg and the MW-induced changes in cell proliferation albeit no such clear correlation was seen at 0.21 mW/kg.

MW exposure of *E. coli* cells and rat thymocytes at PDs of 10^{-5}-10^{-3} W/cm^2 resulted in significant changes in chromatin conformation if exposure was performed at resonance frequencies during 5-10 min[33, 43, 65]. Decrease in the MW effects due to lowering the PD by orders of magnitude down to 10^{-14}-10^{-17} W/cm^2 was compensated by several-fold increase of exposure time to 20-40 min[57]. At the relatively longer duration of exposure, more than 1 h, the same effect at the lowest PD of 10^{-19} W/cm^2 was observed[57].

Gapeyev *et al.* found the frequency and power dependence of anti-inflammatory effect of low-intensity MW exposure (0.1 mW/cm^2) using the model of acute zymosan-induced footpad edema in mice[47]. Single whole-body MW exposure of mice at the frequencies of 42.2, 51.8, and 65 GHz after zymosan injection reduced both the footpad edema and local hyperthermia. Some other frequencies from the frequency range of 37.5-70 GHz were less effective or not effective at all. At the frequency of 42.2 GHz the effect had sigmoid dependence on exposure duration with a maximum at 20-80 min. A linear dependence with significantly lower increment was observed at a 10-fold less intensity (0.01 mW/cm^2). However, this decrease in the effect was compensated by a slight increase in duration of exposure from 80 min to 120 min.

The MW effects on *E. coli* cells depended on the post-exposure time[56-58]. This dependence had an initial phase of increase about 100 min post-exposure followed by a phase, which was close to a plateau, around 100 min. A trend to decrease in effect was observed at longer times up to 300 min[56, 58].

Significant MW-induced changes in chromatin conformation were observed when rat thymocytes were analyzed in-between 30-60 min after exposure to MW[43]. This effect nearly disappeared if the cells were incubated more than 80 min between exposure and analysis.

Gapeev *et al.* have studied dependence of the MW effect on the function of the mouse peritoneal neutrophils in dependence on duration of exposure at the frequency of 41.95 GHz and the PD of 240 μW/cm^2 [45, 46]. This dependence had a bell-shaped form with the maximal effects at 20 - 40 min of exposure.

In recent studies, human lymphocytes from peripheral blood of healthy and hypersensitive to EMF persons were exposed to MW from the GSM mobile phones[38, 39]. MW induced changes in chromatin conformation similar to those induced by heat shock, which remained up to 24 h after exposure. It was found in the same and following studies that GSM MW at the carrier frequency of 915 MHz and UMTS (Universal Mobile Telecommunications System) MW at 1947.4 MHz inhibited formation of 53BP1/γ-H2AX DNA repair foci and these adverse effects remained at 72 h after an 1-h exposure[38, 39, 49].

Of note is that prolonged MW exposures were associated with less prominent effects than shorter exposures in some studies[51, 66, 67]. This type of dependence on exposure duration was explained by adaptation of the exposed systems to the MW exposure[67].

The data indicate that there is a time window for observation of the NT MW effects, which may be dependent on endpoint measured, cell type, duration and PD of exposure. The data from different groups suggest also that duration of exposure may have a larger role for some NT MW effects than PD/SAR.

Coherence time

MW exposure of L929 fibroblasts was performed by the group of Litovitz[68]. MW at 915 MHz modulated at 55, 60, or 65 Hz approximately doubled ornithine decarboxylase

(ODC) activity after 8 h. Switching the modulation frequency from 55 to 65 Hz at coherence times of 1.0 s or less abolished enhancement, while times of 10 s or longer provided full enhancement. These results suggested that the microwave coherence effects are remarkably similar to those observed previously with extremely low frequency (ELF) magnetic fields by the same authors.

Intermittence

Diem and colleagues exposed cultured human diploid fibroblasts and cultured rat granulosa cells to intermittent and continuous MW (1800 MHz; SAR 1.2 or 2 W/kg; different modulations; during 4, 16 and 24 h; intermittent 5 min on/10 min off or continuous exposure)[69]. Comet assay was applied to analyze DNA single- and double-strand breaks. MW-induced effects occurred after 16 h exposure in both cell types and after different mobile-phone modulations. The intermittent exposure showed a stronger effect than continuous exposure.

Remondini *et al.* analyzed changes in gene expression in human HL-60 leukemia cells using gene microarrays[53]. Cells were exposed to MW (SAR 1.0-1.3 W/kg, 1800 MHz DTX mode, 24 h exposure) either continuously or intermittently, 5 min ON/5 min OFF. Gene expression was affected by intermittent exposure but not continuous exposure.

Modulation

There is strong experimental evidence for the role of modulation in the diverse biological effects of NT MW both *in vitro* and *in vivo*[32, 60, 70-79]. Examples include different types of modulation such as amplitude-, speech and phase modulations: (i) Amplitude modulation at 16 Hz, but not 60 Hz or 100 Hz, of a 450-MHz MW increased activity of ODC[74]. (ii) Speech-modulated 835-MHz MW produced no effect on ODC as compared to the typical signal from a TDMA (Time Division Multiple Access) digital cellular phone[71]. (iii) Phase-modulated GSM-1800 MW (Gaussian Minimum Shift Keying, GMSK) at 1.748 GHz induced micronuclei in human lymphocytes while CW MW did not[75].

Gapeev and co-authors studied production of reactive oxygen species (ROS) in isolated peritoneal neutrophils of mice using a model of synergistic reaction of calcium ionophore A23187 and phorbol ester PMA[79, 80]. MW exposure at 41.95 GHz, continuous wave mode and 50 $\mu W/cm^2$, inhibited ROS production. MW modulated with the frequency of 1 Hz resulted in stimulation of the synergistic reaction. Modulation frequencies of 0.5, 2, 4, and 8 Hz did not cause significant effects, and modulation frequencies of 0.1, 16, and 50 Hz inhibited the synergistic reaction.

In other study, Gapeev *et al.* analyzed acute zymosan-induced paw edema in mice[48]. MW exposure of animals at the PD of 0.1- 0.7 mW/cm^2 and some "effective" frequencies in the range of 42-43 GHz decreased the paw edema. Application of different modulation frequencies from the range of 0.03–100 Hz to MW exposure at the effective carrier frequency of 42.2 GHz did not lead to considerable changes in the effect. In contrast, modulation of MW at the ''ineffective'' carrier frequencies of 43.0 and 61.22 GHz by frequencies from the ranges of 0.07–0.1 and 20–30 Hz resulted in a maximal anti-inflammatory effects. The results suggested a complex dependence of

the anti-inflammatory action of low-intensity MW on carrier and modulation frequencies.

Huber with co-authors investigated effects of MW similar to those used in mobile communication, a "base-station-like" and a "handset-like" signal (10 g tissue-averaged spatial peak-SAR of 1 W/kg for both conditions), on waking regional cerebral blood flow (rCBF) in 12 healthy young men[76]. The effect depended on the spectral power in the amplitude modulation of the carrier frequency such that only "handset-like" MW exposure with its stronger low-frequency components but not the "base-station-like" MW exposure affected rCBF. This finding supported previous observations of these authors[77] that pulse modulation of MW is of importance for changes in the waking and sleep EEG, and substantiated the notion that pulse modulation is crucial for MW-induced alterations in brain physiology.

Markkanen *et al.* exposed cdc48-mutated *Saccharomyces cerevisiae* yeast cells to 900 or 872 MHz MW, with or without exposure to ultraviolet (UV) radiation, and analyzed apoptosis[78]. Amplitude modulated (217 pulses per second) MW significantly enhanced UV induced apoptosis in cells, but no effect was observed in cells exposed to unmodulated fields at the identical time-average SAR of 0.4 W/kg that was lower than the ICNIRP safety standards.

Persson and colleagues studied effects of MW of 915 MHz as CW and pulse-modulated with different pulse power and at various time intervals on permeability of the blood-brain barrier (BBB) in Fischer 344 rats[60]. Albumin and fibrinogen were demonstrated immunochemically and classified as normal versus pathological leakage. The CW-pulse power varied from 0.001 W to 10 W and the exposure time from 2 min to 960 min. The frequency of pathological rats significantly increased in all exposed rats. Grouping the exposed animals according to the level or specific absorption energy (J/kg) gave significant difference in all levels above 1.5 J/kg. The exposure was 915 MHz MW either pulse modulated at 217 Hz with 0.57 ms pulse width, at 50 Hz with 6.6 ms pulse width, or CW. The frequency of pathological rats was significantly higher in MW-exposed groups than in controls and the frequency of pathological rats after exposure to pulsed radiation was significantly less than after exposure to CW.

In a study by Lopez-Martin *et al.*[81], GSM-exposed picrotoxin-pretreated rats showed differences in clinical and EEG signs, and in c-Fos expression in the brain, in comparison to picrotoxin-treated rats exposed to an equivalent dose of unmodulated radiation. Neither MW exposure caused tissue heating, so thermal effects could be ruled out. The most marked effects of GSM MW on c-Fos expression in picrotoxin-treated rats were observed in limbic structures, olfactory cortex areas and subcortical areas, the dentate gyrus, and the central lateral nucleus of the thalamic intralaminar nucleus group. Nonpicrotoxin-treated animals exposed to unmodulated radiation showed the highest levels of neuronal c-Fos expression in cortical areas. These results suggested a specific effect of the pulse GSM modulation on brain activity of a picrotoxin-induced seizure-proneness rat model.

Luukkonen *et al.*[82] investigated effects of MW at 872 MHz and relatively high SAR value (5 W/kg) on intracellular reactive oxygen species (ROS) production and DNA damage in human SH-SY5Y neuroblastoma cells. The experiments also involved combined exposure to MW and menadione, a chemical inducing intracellular ROS production and DNA damage. Both CW and a pulsed signal similar to that used in GSM mobile phones were used. Exposure to the CW radiation increased DNA breakage in comparison to the cells exposed only to menadione. Comparison of the same groups also

showed that ROS level was higher in cells exposed to CW RF radiation at 30 and 60 min after the end of exposure. No effects of the GSM-like modulated signal were seen on either ROS production or DNA damage.

Hinrikus *et al.*[83] evaluated the effects of MW (450 MHz) pulse-modulated at the frequencies of 7, 14 and 21 Hz on human electroencephalographic (EEG) rhythms. The field power density at the scalp was 0.16 m W/cm^2. Modulated microwaves caused an increase in the average EEG alpha (17%) and beta (7%) power but the theta rhythm remained unaffected. Increases in the EEG alpha and beta power were statistically significant during the first half-period of the exposure interval (30 s) at the modulation frequencies of 14 and 21 Hz. The authors concluded that the effect of the 450-MHz MW modulated at 7, 14 and 21 Hz varies depending on the modulation frequency.

Hoyto *et al.*[84] exposed human SH-SY5Y neuroblastoma and mouse L929 fibroblast cells to MW (SAR of 5 W/kg) at 872 MHz using continuous-waves (CW) or a modulated GSM-like signal under isothermal conditions[83]. Menadione was used to induce reactive oxygen species, and tert-butylhydroperoxide (t-BOOH) was used to induce lipid peroxidation. Two statistically significant differences related to MW exposure were observed: Lipid peroxidation induced by t-BOOH was increased in SH-SY5Y (but not in L929) cells, and menadione-induced caspase 3 activity was increased in L929 (but not in SH-SY5Y) cells. Both differences were statistically significant only for the GSM-modulated signal.

Franzellitti *et al.*[85] exposed human trophoblast HTR-8/SVneo cells to MW at 1.8 GHz CW and differently modulated GSM signals (GSM-217Hz and GSM-Talk) during 4 - 24 h[84]. The inducible HSP70C transcript was significantly enhanced after 24 h exposure to GSM-217 Hz signals while being reduced after 4 and 16 h exposure to GSM-Talk signal.

Significant amount of *in vivo* studies under varying parameters of exposure (intensity, frequency, exposure time, modulation, intermittence) have been performed in Russia/Soviet Union and published in Russian. Retrospective analysis of 52 Russian/Soviet *in vivo* studies with animals (mice, rats, rabbits, guinea pigs) on chronic exposure to MW has recently been published[11]. In these studies, various endpoints were measured up to 4 month of chronic exposure including analysis of: weight of animal body, histological analysis and weight of tissues, central nervous system, arterial pressure, blood and hormonal status, immune system, metabolism and enzymatic activity, reproductive system, teratogenic and genetic effects. Based on their analysis, the authors concluded that: "exposure to modulated MW resulted in bioeffects, which can be different from the bioeffects induced by CW MW; exposure to modulated MW at low intensities (non-thermal levels) could result in development of unfavorable effects; direction and amplitude of the biological response to non-thermal MW, both *in vitro* and *in vivo*, depended on type of modulation; often, but not always, modulated MW resulted in more pronounced bioeffects than CW MW; the role of modulation was more pronounced at lower intensity levels".

One review of the Russian/Soviet studies on the role of modulation on MW effects is available in English[15]. The authors conclude that "a number of good-quality studies have convincingly demonstrated significant bioeffects of pulsed MW. Modulation often was the factor that determined the biological response to irradiation, and reactions to pulsed and CW emissions at equal time-averaged intensities in many cases were substantially different".

In conclusion, significant amount of in vitro and in vivo studies from different research groups, although not universally reported, clearly indicated dependence of the MW effects on modulation.

Polarization

It is believed that circular polarization might have been important in inducing chiral asymmetry in interstellar organic molecules that could be subsequently delivered to the early Earth and could explain the origin of the chirality of biological molecules[86].

The effects of circularly polarized (CP) MW were studied in *E. coli* cells at the frequencies from two frequency windows (resonances) that were identified using linearly polarized (LP) MW, within the frequency ranges of 51.62-51.84 GHz and 41.25-41.50 GHz[34, 65]. At the resonance frequency of 51.76 GHz, right-handed CP MW inhibited repair of X-ray-induced DNA damages[34, 65]. In contrast to right-handed polarization, left-handed CP MW had virtually no effect on the DNA repair, while the efficiency of LP MW was in-between of two circular polarizations. Inversion in effectiveness of circular polarizations was observed at another resonance frequency, 41.32 GHz. In contrast to the frequency of 51.76 GHz, left-handed CP MW at 41.32 GHz significantly inhibited DNA repair, while right polarization was almost ineffective. MW of the same CP affected cells at several frequencies tested within each resonance, alternative CP being almost ineffective[34, 54, 65]. Therefore, specific sign of effective CP, either left- or right-, was the attribute of each resonance. Two different types of installations, based on either spiral waveguides[65] or quarter-wave mica plates[34, 41, 54, 87, 88], were used to produce CP MW. Similar results were observed regardless the way of producing the MW of different polarizations.

Pre-irradiation of *E. coli* cells to X-rays inverted the sign of effective polarization[34, 54]. This inversion was observed for two different resonances, 41.32 and 51.76 GHz. Neither resonance frequencies, nor half-widths of the resonance changed during the inversions in effective CPs. The effects of left- and right-handed CP MW become the same at 50 cGy[34]. At this dose, about one single stranded DNA break per haploid genome was induced. X-ray-induced DNA breaks result in relaxation of the supercoiled DNA-domains. It is known that the majority of DNA in living cells has a right-handed helicity (B-form) but a minor part, in order of 1 %, may alternate from the B-form with the form of left-handed helix (Z-form). Supercoiling is connected with transitions between right B-form to left Z-form in these DNA sequences. Therefore, the data suggested that difference in biological effects of polarized MW might be connected with DNA helicity and supercoiling of DNA-domains.

Supercoiling of DNA-domains is changed during cell cycle because of transcription, replication, repair, and recombination. It can also be changed by means of DNA-specific intercalators such as ethidium bromide (EtBr). EtBr changes supercoiling and facilitates the transition of DNA sequences from Z-form to B-form. Preincubation of *E. coli* AB1157 cells with EtBr inverted the effective polarization at the resonance frequency of 51.755 GHz and right-handed MW became more effective than left polarization[87]. EtBr changed the supercoiling of DNA-domains starting at a concentration of 1 μg/ml as measured with the AVTD in different cell types including *E. coli*[35, 37, 89]. These data provided further evidence that DNA may be a target for the NT MW effects.

The effects of MW on conformation of nucleoids in *E. coli* cells have recently been studied at the power flux density of 100 μW/cm^2 [90]. Linearly polarized MW resulted in significant effects within specific frequency windows of resonance type in the range of 51-52 GHz. The distances between frequency windows were about 55-180 MHz. Only one of the two possible circular polarizations, left-handed or right-handed, was effective at each frequency window. The sign of effective circular polarization alternated between frequency windows.

While most data on polarization have been obtained by the same research group[34, 41, 43, 54, 56, 65, 87, 88, 90-92], recent data of others corroborated our findings at least partially[93]. These authors analyzed the condensation of chromatin in human buccal epithelium cells by the method of vital indigo carmine staining. MW induced chromatin condensation in dependence on polarization[93].

Obviously, the difference in effects of right- and left polarizations could not be explained by the heating or by the mechanism dealing with "hot-spots" due to unequal SAR distribution. The data about the difference in effects of differently polarized MW, the inversion of effective circular polarization between resonances and after irradiation of cells with X-rays and incubation with EtBr provided strong evidence for the non-thermal mechanisms of MW effects. These data suggested chiral asymmetry in the target for the NT MW effects, one of which is presumably chromosomal DNA[34], and selection rules on helicity if quantum-mechanical approach is applied[54].

Electromagnetic environment

Hypothetically, background EMF might be of importance for the MW effects. This hypothesis is based on the experimental observations that SMF, ELF magnetic fields, and MW at low intensities induced similar effects in cells under specific conditions of exposure[1, 39, 94-96]. Despite very little has been achieved for mechanistic explanation of such effects, there are attempts to consider the effects of EMF in a wide frequency range in the frames of the same physical models[97-103].

Litovitz and colleagues found that the ELF magnetic noise inhibited the effects of MW on ODC in L929 cells[72]. The ODC enhancement was found to decrease exponentially as a function of the noise root mean square amplitude. With 60 Hz amplitude-modulated MW, complete inhibition was obtained with noise levels at or above 2 μT. With the DAMPS (Digital Advanced Mobile Phone System) cellular phone MW, complete inhibition occurred with noise levels at or above 5 μT. Further studies by the same group revealed that the superposition of ELF noise inhibited hypoxia de-protection caused by long term repeated exposures of chick embryos to MW[104].

The effect of a magnetic noise on microwave-induced spatial learning deficit in the rat was investigated by Lai[105]. Rats were exposed to MW (2450 MHz CW, PD 2 mW/cm^2, average whole-body SAR 1.2 W/kg) alone or in combination with noise exposure (60 mG). Microwave-exposed rats had significant deficit in learning. Exposure to noise alone did not significantly affect the performance of the animals. However, simultaneous exposure to noise significantly attenuated the microwave-induced spatial learning deficit. The author concluded that simultaneous exposure to a temporally incoherent magnetic field blocks MW-induced spatial learning and memory deficits in the rat[105].

Lai and Singh studied combined effects of a temporally incoherent magnetic noise (45 mG) and MW (CW 2450 MHz, PD 1 mW/cm^2, average whole-body SAR of 0.6

W/kg) in rat brain cells[106]. MW exposure induced significant DNA breakages as measured with both neutral and alkaline comet assays. Exposure to noise alone did not significantly affect cells. However, simultaneous noise exposure blocked the MW-induced effects.

Yao and colleagues investigated the influence of the GSM-like MW at 1.8 GHz on DNA damage and intracellular reactive oxygen species (ROS) formation in human lens epithelial cells (hLECs)[107]. DNA damage examined by alkaline comet assay was significantly increased after 3 W/kg and 4 W/kg radiation, whereas the double-strand breaks (DSB) evaluated by γ-H2AX foci were significantly increased only after 4 W/kg radiation. Significantly elevated intracellular ROS levels were detected in the 3-W/kg and 4-W/kg groups. After exposure to 4 W/kg for 24 hours, hLECs exhibited significant G_0/G_1 arrest. All the effects were blocked when the MW exposure was superposed with a 2 μT electromagnetic noise. The authors concluded that superposed electromagnetic noise blocks MW-induced DNA damage, ROS formation, and cell cycle arrest.

We have previously reported that resonance effects of MW on *E. coli* cell depend on the magnitude of static magnetic field at the place of MW exposure[57]. This dependence was explained by the model of electron-conformational interactions that also predicted possible shift of resonance frequencies in dependence on SMF[35]. More recently, Ushakov with co-authors exposed *E. coli* cells to MW at the PD of 10^{-10} W/cm^2 and the frequencies of 51.675, 51.755 and 51.835 GHz[88]. In this study, cells were exposed to MW at various values of SMF: 22, 49, 61, or 90 μT. The authors observed that the effects of MW exposure on the conformation of nucleoids depended on the SMF during exposure.

Gapeev *et al.* analyzed effects of MW (41.85-42.1 GHz, frequency increment 50 MHz, PD 50 μВт/cm^2, 20 min exposure) on synergistic reaction of calcium ionophore A23187 and phorbol ester PMA in activation of the respiratory burst of the peritoneal neutrophils of mice[79]. The MW exposure was performed at various SMF. At a SMF of 50 μT, the authors observed frequency-dependent inhibition of the synergetic reaction with maximal effect at the frequency of 41.95 GHz. In the same frequency range, frequency-dependent activation of the synergetic reaction with a maximal effect at the frequency of 42.0 GHz was found at a SMF of 95 μT. The authors concluded that increasing the SMF from 50 to 95 μT resulted in the inversion of ten MW effects and the shift of the resonance frequency by 50 MHz[79, 108]. Moreover, these effects of MW at the 41.95 GHz and 42.0 GHz were not found at the SMF of ±1, 28.3, 75.5 or 117.3 μT suggesting that the NT MMW effects may appear only at specific values of SMF[79, 108].

The observations on dependence of the NT MW effects on SMF and ELF stray field may be of significant interest for further development of physical theory for the NT MW effects and development of safe mobile communication.

Cell-to-cell interaction in response to NT MW

The effects of NT MW at the resonance frequency of 51.755 GHz on conformation of nucleoids in *E. coli* cells were analyzed with respect to cell density during exposure[57]. The per-cell-normalized effect of MW increased by a factor of 4.7±0.5 on average as cell density increased by one order of magnitude, from $4 \cdot 10^7$ to $4 \cdot 10^8$ cell/ml. These data suggested a co-operative nature of cell response to MW, which is based on cell-to-cell

interaction during exposure. This suggestion was in line with the observed partial synchronization of cells after exposure to MW.

The co-operative nature of cell response to MW at the resonance frequency of 51.755 GHz was confirmed in further studies with *E. coli* cells[35, 41, 58]. In addition, dependence of the per-cell-normalized effect on cell density was found for two other resonances, 51.675 GHz and 51.688 GHz. These data suggested that dependence on cell density during exposure is a general attribute of the resonance response of *E. coli* cells to NT MW. At the cell density of $4 \cdot 10^8$ cells/ml, the average intercellular distance was approximately 13 μm that is 10 times larger than the linear dimensions of *E. coli* cells[57, 58]. Therefore, no direct physical contact seemed to be involved in the cell-to-cell interaction. Two mechanisms, biochemical and electromagnetic, were considered to account for the co-operative nature in the resonance response to weak EMF in wide frequency range including ELF, MW and ionizing radiation[57, 109, 110]. The first one, biochemical, is based on release of secondary chemical messengers (ions, radicals, or molecules) by those cells, which were directly targeted. Via diffusion, these messengers can induce response in other cells. The second mechanism, electromagnetic, is based on reemission of secondary photons. According to this mechanism, reemitted photons can induce response in other cells if the intercellular distance is shorter than the length of photon absorption. Our experimental data on MW effects fitted better to the electromagnetic mechanism but a combination of two mechanisms was also possible[57, 58]. In particular, free radicals with prolonged lifetimes might be involved in the observed cell-to-cell communication during response to EMF[111].

The absorption length of photons with the frequencies of 10^{12}-10^{13} Hz corresponds to the intracellular distance at the cell density of $5 \cdot 10^8$ cell/ml, at which saturation in the dependences of EMF effects on cell density was observed[57, 58, 111, 112]. Such photons may be involved in cell-to-cell communication according to the electromagnetic mechanism and in agreement with the prediction of Fröhlich that biosystems support coherent excitations within frequency range of 10^{11}-10^{12} Hz[44]. From this point of view, cell suspension may respond to NT MW as a whole. In this case, the number of the exposed cells should be large enough to facilitate cell-to-cell communication during the responses to MW at specific parameters of exposure such as frequency, modulation, and polarization. Interestingly, the cell density for saturation of both MW and ELF effects was about $5 \cdot 10^8$ cell/ml that is close to cell densities in soft tissues of eukaryotes[58, 111]. Such density of cells in the tissues may be important for regulation of living systems by electromagnetic cell-to-cell communication. Cellular membranes and DNA have been considered as possible sources of coherent excitations and photons, which may be involved in electromagnetic cell-to-cell communication[35, 44, 111].

PD dependences of the MW effect at the 51.755 GHz resonance frequency were considerably different between two cell densities, $4 \cdot 10^7$ cells/ml and $4 \cdot 10^8$ cells/ml[35]. However, the resonance frequency of 51.755 GHz did not shift with the changes in cell density. The half-width of the 51.755 GHz resonance did not depend on cell density either. Contrary to the 51.755 GHz resonance response, the half-width of the 51.675 GHz resonance depended on cell density[41]. The data suggested that intracellular interaction during the NT MW exposures at some specific frequencies might affect sub-cellular targets for NT MW. This target is presumably chromosomal DNA that is organized in the DNA-domains[34, 92, 97].

In all studies concerning dependence of the MW effects on cell density, the cells occupied a negligible part of the exposed volume and could not change the absorption

of MW even at the highest cell densities[35, 41, 57, 58]. Striking difference in the cell responses at various cell densities provided further evidence for non-thermal mechanism of the observed MW effects.

Significant MW effect on synchronization of *Saccharomyces carlsbergensis* yeast cells were observed by Golant and co-authors[113]. Exposure to MW at 30 μW/cm^2 and 46 GHz induced synchronization as measured by cell density and bud formation. The authors assumed that MW induced cell-to-cell interaction resulting in the observed synchronization.

Genetic background and cell type

We studied effects of MW on *E. coli* cells of three isogenic strains with different length of chromosomal DNA[92]. Bacterial chromosomal DNA in N99 wild type cells was lengthened by inserting DNA from λ and λ*imm*^{434}*bio*^{10} phages. Lysogenic strains N99(λ) and N99(λ,λ*imm*^{434}*bio*^{10}) obtained were used for MW exposure along with the wild type N99 strain. The response of each strain was studied at 10-17 frequencies within the ranges of 41.24-41.37 GHz and 51.69-51.795 GHz. Clear resonance responses to MW at 10^{-10} W/cm^2 were observed for each strain in both frequency ranges. Significant shifts of both resonance frequencies were found between strains. The shifted resonances had the same amplitude and half-width as for N99 cells[92]. Upon shifting, no changes in effective circular polarization within each shifted resonance were observed. The shifts in resonance frequencies could not be explained by activity of additional genes inserted with the phage DNA. On the other hand, the theoretical consideration based on oscillations of the DNA-domains regarding a whole nucleoid provided a good correlation between the increasing in the DNA length and the shifts in resonances[92].

A detailed analysis of MW effects on *E. coli* AB1157 cells at 10^{-10} W/cm^2 and various frequencies revealed the resonance frequency of 51.755±0.001 GHz[35]. This value was statistically significantly different from the resonance frequency of 51.765±0.002 in response of *E. coli* N99 cells to MW in the same frequency range[35]. It should be noted that both strains, AB1157 and N99, are considered as wild type strains. Nevertheless, these strains are different in their genotypes by several specific gene markers[23, 33]. These data suggested that strains of different origin, even being considered as wild type strains, might have different resonance responses to NT MW.

Stagg with colleagues exposed tissue cultures of transformed and normal rat glial cells to packet-modulated MW (TDMA that conforms to the North American digital cellular telephone standard) at 836.55 MHz[114]. Results from DNA synthesis assays differed for these two cell types. Sham-exposed and MW-exposed cultures of primary rat glial cells showed no significant differences for either log-phase or serum-starved condition. C6 glioma cells exposed to MW at 5.9 μW/g SAR (0.9 mW/cm^2) exhibited small (20-40%) but significant increases in 38 % of [^{3}H]-thymidine incorporation experiments.

Repacholi with co-authors chronically exposed wild-type mice and E mu-Pim1 transgenic mice, which are moderately predisposed to develop lymphoma spontaneously, to plane-wave pulse-modulated MW at 900 MHz with a pulse repetition frequency of 217 Hz and a pulse width of 0.6 ms[115]. Incident power densities were 2.6-13 W/m^2 and SARs were 0.008-4.2 W/kg, averaging 0.13-1.4 W/kg. The lymphoma risk was found to be

significantly higher in the exposed transgenic mice. No effects were seen in the wild type mice.

Markkanen with colleagues found that MW affected the UV-induced apoptosis in *Saccharomyces cerevisiae* yeast cells KFy437 (cdc48-mutant) but did not modify apoptosis in KFy417 (wild-type) cells[78].

Czyz with colleagues exposed pluripotent embryonic stem (ES) cells of wild-type and deficient for the tumor suppressor p53 to pulse modulated GSM MW at 1.71 GHz[116]. Two dominant GSM modulation schemes (GSM-217 and GSM-Talk), which generate temporal changes between GSM-Basic (active during talking phases) and GSM-DTX (discontinuous transmission, which is active during listening phases thus simulating a typical conversation), were applied to the cells at and below the ICNIRP safety standards. GSM-217 MW induced a significant upregulation of mRNA levels of the heat shock protein hsp70 of p53-deficient ES cells differentiating in vitro, paralleled by a low and transient increase of c-jun, c-myc, and p21 levels in p53-deficient, but not in wild-type cells. Theses data substantiated the notion that the genetic background determines cellular responses to GSM MW.

Human cultured fibroblasts of three different donors and three different short-term human lymphocyte cultures were exposed to UMTS-like MW at 1950 MHz and the SAR below safety limit of 2 W/kg by Schwarz *et al.*[117]. The alkaline comet assay and the micronucleus assay were used to analyze genotoxic effects. UMTS exposure increased the comet tail factor (CTF) and induced centromere-negative micronuclei in human cultured fibroblasts in a dose and time-dependent way. No UMTS effect was obtained with lymphocytes, either unstimulated or stimulated with phytohemagglutinin. The authors concluded that UMTS exposure may cause genetic alterations in some but not in all human cells in vitro.

Hoyto *et al.*[118], analyzed the effects of MW exposure on cellular ornithine decarboxylase (ODC) activity in fibroblasts, two neural cell lines and primary astrocytes. Several exposure times and exposure levels were used, and the fields were either unmodulated or GSM-like-modulated. Murine L929 fibroblasts, rat C6 glioblastoma cells, human SH-SY5Y neuroblastoma cells, and rat primary astrocytes were exposed to RF radiation at 872 MHz in a waveguide exposure chamber equipped with water cooling. Cells were exposed for 2, 8, or 24 hours to CW MW or to a GSM type signal pulse modulated at 217 Hz. ODC activity in rat primary astrocytes was decreased statistically significantly and consistently in all experiments performed at two exposure levels (1.5 and 6.0 W/kg) and using GSM modulated or CW radiation. In the secondary cell lines, ODC activity was generally not affected. The authors concluded that ODC activity was affected by MW exposure in rat primary neural cells, but the secondary cells used in this study showed essentially no response. In further studies by the same group, the difference in response of human SH-SY5Y neuroblastoma and mouse L929 fibroblast cells to a GSM-modulated MW at 872 MHz was documented[84].

Nylund and Leszczynski have examined cell response to MW (900 MHz GSM-like signal, average SAR of 2.8 W/kg) using two human endothelial cell lines: EA.hy926 and EA.hy926v1[119]. Gene expression changes were examined using cDNA Expression Arrays and protein expression changes were examined using 2-DE and PDQuest software. The same genes and proteins were differently affected by exposure in each of the cell lines.

Remondini *et al.* analyzed changes in gene expression in six human cell lines by gene microarrays[53]. Cells were exposed to MW at 900 MHz GSM Basic mode, SAR 1.8-2.5

W/kg, 1 h exposure. Most cell lines responded to GSM-900 MHz, except for the CHME5 human microglial cells.

Zhao *et al.* studied whether expression of genes related to cell death pathways are dysregulated in primary cultured neurons and astrocytes by exposure to MW from GSM cell phone at the frequency of 1900 MHz for 2 h[120]. Microarray analysis and real-time RT-PCR have shown up-regulation of caspase-2, caspase-6 and Asc (apoptosis associated speck-like protein containing a card) gene expression in neurons and astrocytes. Up-regulation occurred in both "on" and "stand-by" modes in neurons, but only in "on" mode in astrocytes. Additionally, astrocytes showed up-regulation of the Bax gene. The authors concluded that even relatively short-term exposure to the cell phone can up-regulate elements of apoptotic pathways in cells derived from the brain, and that neurons appear to be more sensitive to this effect than astrocytes.

Finally, it follows from the emerging data that MW effects are defined by the genotype and may be cell-type and cell-line dependent. These dependences may explain, at least partly, the discrepancies among replication studies from different laboratories.

Gender- and age-related differences

There are studies indicating that MW may exert a gender-related influence on brain activity[121-123]. Papageorgiou and co-authors investigated the gender-related influence of MW similar to that emitted by GSM900 mobile phones on brain activity[121]. Baseline EEG energy of males was greater than that of females, and exposure to MW decreased EEG energy of males and increased that of females. Memory performance was invariant to MW exposure and gender influences. Smythe and Costall reported the effects of mobile phone exposure on short- and long-term memory in male and female subjects[122]. The results showed that males exposed to an active phone made fewer spatial errors than those exposed to an inactive phone condition, while females were largely unaffected. These results further indicated that mobile phone exposure has functional consequences for human subjects, and these effects appear to be gender-dependent. Nam and colleagues exposed volunteers of both gender to MW emitted by a CDMA cellular phone for half an hour[123]. Physiological parameters such as systolic and diastolic blood pressures, heart rate, respiration rate, and skin resistance were simultaneously measured. All the parameters for both groups were unaffected during the exposure except for decreased skin resistance of the male subjects[123].

Prevalence of women (usually around 70%) among subjects, which report hypersensitivity to electromagnetic fields of wide frequency range including MW, may also be considered as an indirect evidence for the gender-dependent effects of MW.

In his pioneering study concerning age in cancer risk from MW exposure, Hardell and colleagues found that the highest risks were associated with >5-year latency period in the 20-29-year age group for analog phones (OR = 8.17, 95% CI = 0.94-71), and cordless phones (OR = 4.30, 95% CI = 1.22-15)[124]. Of note, no participants of age less 20 years were involved on this study. In further studies from the Hardell's group, highest risk was found in the age group <20 years at time of first use of wireless phones[125, 126].

Nam with co-authors reported that skin resistance in teenagers decreased by exposure to CDMA MW from cellular phones whereas no effects were seen in adults[123].

Individual differences

We observed significant individual variations in effects of GSM and UMTS MW on chromatin conformation and 53BP1/γ-H2AX DNA repair foci in studies with lymphocytes from hypersensitive to EMF subjects and healthy persons[38-40, 49].

Shckorbatov with colleagues investigated electrokinetic properties of cell nuclei and condensation of heterochromatin in human buccal epithelium cells in response to MW at 42.2 GHz[127]. MW exposure decreased electric charge of cell nuclei and an increased chromatin condensation in dependence on individual traits of donors[127].

Hinrikus *et al.*[83] evaluated the effects of pulse-modulated MW (450 MHz) on human EEG rhythms. Thirteen healthy volunteers were exposed to MW; the field power density at the scalp was 0.16 m W/cm^2. Differences were found in individual sensitivity to exposure. Increases in the EEG beta power appeared statistically significant in the case of four subjects. In other study, the same authors confirmed and extended their observations on individual sensitivity to exposure with pulse-modulated MW[128]. The experiments were carried out on four different groups of healthy volunteers. A 450-MHz MW modulated at 7 Hz (first group), 14 and 21 Hz (second group), 40 and 70 Hz (third group), 217 and 1000 Hz (fourth group) frequencies was applied. MW exposure, SAR 0.303 W/kg, increased the EEG energy. The proportion of subjects significantly affected was similar in all groups except for the 1000 Hz group: in the first group 16% at 7 Hz modulation; in the second group 31% at 14 Hz modulation and 23% at 21 Hz modulation; in the third group 20% at 40 Hz and 13% at 70 Hz modulation; in the fourth group 16% at 217 Hz and 0% at 1000 Hz modulation frequency.

Zotti-Martelli with colleagues exposed peripheral blood lymphocytes from nine different healthy donors for 60, 120 and 180 min to CW MW with a frequency of 1800 MHz and PD of 5, 10, and 20 mW/cm^2 and analyzed DNA damage using micronucleus (MN) assay[129]. Both spontaneous and induced MN frequencies varied in a highly significant way among donors, and a statistically significant increase of MN, although rather low, was observed dependent on exposure time and PD. The data analysis highlighted a wide inter-individual and reproducible variability in the response.

Sannino *et al.* evaluated the induction of micronuclei in response to MW (900 MHz, average SAR of 1.25 W/kg) exposure and subsequent treatment with mitomycin C in peripheral blood lymphocytes from five human volunteers[130]. MW exposure reduced the level of mitomycin C –induced micronuclei in cells collected from four donors (i.e., responders). However, the effect of MW was not observed in the remaining donor (i.e., non-responder). The overall data indicated the existence of heterogeneity in the MW response among individuals.

Physiological variables

The importance of physiological variables, which may include all conditions of cell culture growth such as aeration, the composition of the growth and exposure media, on NT MW effects has previously been reviewed[8].

In our investigations, *E. coli* cells were exposed to CP or LP MW (100 μW/cm^2) at the resonance frequencies of 41.32 GHz and 51.76 GHz[56, 57]. Both value and direction of the MW effects strongly depended on the phase of culture growth. At logarithmic phase of growth, MW resulted in condensation of nucleoids. In contrast, MW exposure decon-

densed nucleoids in cells if exposure was performed at the stationary phase of growth. It is known, that the state of nucleoid condensation depends on cell activity. In stationary cells nucleoids are more condensed compared to logarithmic cells that divide actively. We concluded that MW are able to either stimulate or inhibit activity of the cells in dependence on stage of growth, stationary or logarithmic, respectively. Higher variability in effects was observed for logarithmic phase and effects were more stable for the stationary phase that is characterized by partial synchronization of cells[56, 57]. There was no effect at all if cells were exposed at the end of the logarithmic phase where the MW effects changed their direction from inhibition to stimulation[57]. Another peculiarity was observed at the very beginning of the logarithmic stage, where the condensation of chromatin induced by MW was very weak. The AVTD data were confirmed by the electrophoretic analysis of proteins bound to DNA[56]. The main feature of the effect in the stationary phase was a decrease in the quantity of several unidentified DNA-bound proteins with molecular weights of 61, 59, 56, 26, and 15 kDa. In contrast, the main trend was an increase in some proteins, 61, 56, 51 and 43 kDa after exposure at the logarithmic phase. The decrease or increase in the level of proteins bound to DNA correlated with the observed changes in the state of nucleoids, decondensation or condensation, respectively.

The MW effects was studied both at stationary and logarithmic phase of growth during exposure to MW in the PD range of 10^{-18} to $3 \cdot 10^{-3}$ W/cm^2 at various cell densities[58]. Relatively weak response to MW was observed in exponentially growing cells. Partially synchronized stationary cells were more sensitive, especially at the cell densities above 10^8 cell/ml. The data suggested that the co-operative responses of cells to MW vary in dependence on phase of growth.

Recent data by Ushakov and colleagues indicated that the MW effects on *E. coli* cells depended on concentration of oxygen in the cell suspension during exposure[88]. This dependence might suggest that oxygen concentration should be indicated in order to improve reproducibility in replication studies.

Similar to the effects of ELF[95], the MW effects were reported to depend on concentration of divalent ions[79].

Antioxidants and radical scavengers inhibit effects of MW

Lai and Singh described effects of MW on the rat brain cells as measured using a microgel electrophoresis assay[131]. These effects were significantly blocked by treatment of rats either with the spin-trap compound N-tert-butyl-α-phenylnitrone or with melatonin that is a potent free radical scavenger and antioxidant[132]. These data suggested that free radicals might be involved in the effects of MW.

Oktem and colleagues exposed rats to MW from GSM900 mobile phone with and without melatonin treatment[133]. Malondialdehyde (MDA), an index of lipid peroxidation, and urine N-acetyl-beta-d-glucosaminidase (NAG), a marker of renal tubular damage, were used as markers of oxidative stress-induced renal impairment. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) activities were studied to evaluate changes in antioxidant status. In the MW-exposed group, while tissue MDA and urine NAG levels increased, SOD, CAT, and GSH-Px activities were reduced. Melatonin treatment inhibited these effects. The authors concluded that melatonin might exhibit a protective effect on mobile phone-induced renal impairment in rats.

Ozguner and colleagues exposed Wistar-Albino rats to MW from GSM900 mobile phone with and without melatonin and analyzed histopathologic changes in skin[134]. MW induced increase in thickness of stratum corneum, atrophy of epidermis, papillamatosis, basal cell proliferation, granular cell layer (hypergranulosis) in epidermis and capillary proliferation. Impairment in collagen tissue distribution and separation of collagen bundles in dermis were all observed in exposed animals as compared to the control group. Most of these changes, except hypergranulosis, were prevented with melatonin treatment. The authors concluded that exposure to GSM900 MW caused mild skin changes and melatonin treatment could reduce these changes. In other studies of the same group, the ability of melatonin to reduce various MW-induced effects was confirmed and inhibitory potential of the antioxidant caffeic acid phenethyl ester (CAPE) was reported[135-138].

Ayata *et al.* analyzed the effects of 900 MHz MW with and without melatonin on fibrosis, lipid peroxidation, and anti-oxidant enzymes in rat skin[139]. The levels of MDA and hydroxypyroline and the activities of SOD, GSH-Px, and CAT were studied. MDA and hydroxyproline levels and activities of CAT and GSH-Px were increased significantly in the exposed group without melatonin and decreased significantly in the exposed group with melatonin. SOD activity was decreased significantly in the exposed group and this decrease was not prevented by the melatonin treatment. The authors assumed that the rats irradiated with MW suffer from increased fibrosis and lipid peroxidation and that melatonin can reduce the fibrosis and lipid peroxidation caused by MW.

Ilhan with co-authors investigated oxidative damage in brain tissue of rats exposed to GSM900 MW with and without pretreatment with Ginkgo biloba (Gb)[140]. MW induced oxidative damage measured as: (i) increase in MDA and nitric oxide (NO) levels in brain tissue, (ii) decrease in brain SOD and GSH-Px activities, and (iii) increase in brain xanthine oxidase and adenosine deaminase activities. These MW effects were prevented by the Gb treatment. Furthermore, Gb prevented the MW-induced cellular injury in brain tissue revealed histopathologically. The authors concluded that reactive oxygen species may play a role in the adverse effects of GSM900 MW and Gb prevents the MW-induced oxidative stress by affecting antioxidant enzymes activity in brain tissue.

Koylu *et al.* studied the effects of MW on the brain lipid peroxidation in rats, and the possible protective effects of melatonin on brain degeneration induced by MW[141]. The levels of lipid peroxidation in the brain cortex and hippocampus increased in the MW group compared with the control group, although the levels in the hippocampus were decreased by combined administration of MW and melatonin. Brain cortex lipid peroxidation levels were unaffected by melatonin treatment. The authors concluded that melatonin may prevent MW-induced oxidative stress in the hippocampus by strengthening the antioxidant defense system.

Sokolovic *et al.* [142] evaluated the intensity of oxidative stress in the brain of Wistar rats chronically exposed to MW from mobile phones (SAR = 0.043-0.135 W/kg) during 20, 40 and 60 days. A significant increase in brain tissue malondialdehyde (MDA) and carbonyl group concentration was found. Decreased activity of catalase (CAT) and increased activity of xanthine oxidase (XO) remained after 40 and 60 days of MW exposure. Melatonin treatment significantly prevented the increases in MDA content and XO activity in the brain tissue after 40 days of exposure while it was unable to prevent the decrease of CAT activity and increase of carbonyl group contents. The authors

concluded that exposure to the mobile phone MW caused oxidative damage in the brain and that treatment with melatonin significantly prevented this oxidative damage.

To conclude this section, several studies suggest that supplementation with antioxidants and radical scavengers can reduce MW effects.

Summary of experimental studies

Numerous experimental data have provided strong evidence for NT MW effects and have also indicated several regularities in appearance of these effects: dependence on frequency within specific frequency windows of "resonance-type"; narrowing of the frequency windows with decreasing intensity; dependence on modulation and polarization; sigmoid dependence on intensity within specific intensity windows including super-low PD comparable to intensities from base stations; thresholds in intensity and exposure time (coherence time); dependence on duration of exposure and post-exposure time; dependence on cell density that suggests cell-to-cell interaction during response to NT MW; dependence on physiological conditions during exposure, such as stage of cell growth, concentration of oxygen and divalent ions, activity of radicals; dependence on genotype; cell-type and cell-line dependence; gender-, age- and individual differences; and SMF and EMF stray field during exposure may be of importance for the effects of NT MW.

Replication studies

Obviously, not taking into account the dependences of NT MW effects on a number of physical parameters and biological variables may result in misleading conclusions regarding the reproducibility of these effects. Especially important might be the observations that NT MW could inhibit or stimulate the same functions dependent on conditions of exposure[2]. Under different conditions of exposure, MW either increased or decreased the growth rate of yeast cells[8], the radiation-induced damages in mice[141], the respiratory burst in neutrophils of mice[79], the condensation of nucleoids in *E coli* cells[56, 57] and human lymphocytes[40]. Potentially bi-directional effects of MW should be taken into account in replication studies.

Despite of considerable body of studies with NT MW in biology, only a few studies were performed to replicate the original data on the NT MW effects. It should be noted, that these replications are usually not completely comparable with the original studies because of either missing description of important parameters of exposure or significant differences in these parameters between original study and replication.

One well-known attempt to replicate the results of Gründler was the study by Gos and co-authors[144]. No MW effects were observed in this replication study. However, the deviations from the Gründler's protocol might be a simple reason for poor reproducibility. For example, synchronized cells were used in studies of Gründler. Contrary to the Gründler's original protocol, Gos used exponentially growing cells. If the MW effects in yeast cells are dependent on stage of growth, cell density and intercellular interactions as it has been described for *E. coli* cells[35, 41, 56, 57], no response should be expected in the logarithmic phase of growth. Gos and colleagues used *S. cerevisiae* strain with the auxotrophy mutations for leucine and uracil. Gründler used the wild type strain. It might suggest another cause for the deviations between the data of Gründler and Gos. Despite

orientation of SMF in respect to electric and magnetic components of MW was the same, the values of SMF were different. The stray ELF field was 120 nT in the study by Gos, that is higher than usually observed background fields, < 50 nT. The spectral characteristics of the background fields, which were described only in the study by Gos, might be also different. In addition, the conditions of cell cultivation might vary between studies; for example, the data on oxygen concentration in media used in both studies are not available.

Amount of already known physical and biological variables that are important for reproducibility of NT MW effects seem to be far beyond the limits of usually controlled parameters in biological experiments. The knowledge of some of these variables is based on consistent findings following from experimental studies of different research groups. Further evaluation of variables that are important for the NT MW effects would benefit from the developing of the physical and molecular biological models for the MW effects.

Most reviews of the experimental studies do not include analysis of various biological variables and physical parameters when comparing the data on NT MW effects from different studies. As result, misleading conclusion is often made that MW at NT levels produce no "reproducible" effects.

Possible mechanisms

Analyzing theoretically our experimental data on the MW effects at super-low intensities we concluded that these effects should be considered using quantum-mechanical approach[57]. Reanalysis of our data by Binhi resulted to the same conclusion[97]. This is in line with the fundamental quantum-mechanical mechanism that has been suggested by Fröhlich[145]. Most probably, the physical mechanisms of the NT MW effects must be based on quantum-mechanical approach and physics of non-equilibrium and nonlinear systems[44, 98, 146-148].

Our data indicated also that chromosomal DNA is a target for interaction with MW[34, 87, 92]. The length of genomic DNA is much longer than the dimension of surrounding compartment. For example, there is about 1.8 m of DNA in a human genome that is compacted in interaction with other compounds such as proteins, RNA and ions to fit into a nucleus with a characteristic diameter of 5-10 μm. Importantly, concentration of DNA in the nuclei is higher than in crystallization solutions for DNA, 50-100 mM versus 10-30 mM, respectively. Whether DNA is organized in nuclei as a liquid crystal remains to be investigated. However, it is clear that DNA in a living cell cannot be considered as an aqueous solution of DNA molecules in a thermodynamic equilibrium.

The quantum-mechanical physical model for primary interaction of MW with DNA has been proposed[149]. We hypothesized that genomic DNA contain two different codes[109]. The first one is the well-known genetic triplet code for coding the genes. The second one is a "physical code" that determine the spectrum of natural oscillations in chromosomal DNA including electromagnetic, mechanical and acoustic oscillations, which are hypothetically responsible for regulation of gene expression at different stages of ontogenesis and for genomic rearrangements in evolution[109]. The physical model describing these coupled oscillations in chromosomal DNA has been proposed[92]. This model helps to resolve the so-called C-paradox that addresses the issue of a genome size, so-called C-value. Only few percent of DNA encodes genes in almost all eukaryotic genomes. The same amount of DNA is involved in regulation of gene expression by known biochemical mechanisms. The function of the rest of DNA, which does not depend on complexity

of eukaryotic species and is represented by noncoding repetitive DNA sequences, is not understood in molecular biology providing a basement for hypotheses such as "junk DNA". The function of this major part of genomic DNA became clear given that the whole genomic DNA is responsible for the creation of the natural spectrum of oscillations that is hypothetically a main characteristic of each biological species[109].

The understanding of mechanisms for the NT MW effects is far from comprehensive. Many questions remain to be addressed such as whether resonance effects of MW depend on electromagnetic noise and SMF during exposure.

Urgent needs and further perspectives

At present, new situation arose when a significant part of the general population is exposed chronically (much longer than previously investigated durations of exposures) to NT MW from different types of mobile communication including GSM and UMTS/3G phones and base stations, WLAN (Wireless Local Area Networks), WPAN (Wireless Personal Area Networks such as Bluetooth), DECT (Digital Enhanced (former European) Cordless Telecommunications) wireless phones. It should be anticipated that some part of the human population, such as children, pregnant women and groups of hypersensitive persons could be especially sensitive to the NT MW exposures.

Multiple sources of mobile communication result in chronic exposure of significant part of general population to MW at the non-thermal levels. Therefore, the ICNIRP safety standards, which are based on thermal effects in acute exposures, cannot protect the general population from the chronic exposures to NT MW from mobile communication[13].

Most of the real signals that are in use in mobile communication have not been tested so far. Very little research has been done with real signals and for durations and intermittences of exposure that are relevant to chronic exposures from mobile communication. In some studies, the so-called "mobile communication-like" signals were investigated that in fact were different from the real exposures in such important aspects as intensity, carrier frequency, modulation, polarization, duration and intermittence. How relevant such studies to evaluation of adverse health effects from MW of mobile communication is not known.

Emerging evidence suggests that the SAR concept, which has been widely adopted for safety standards, may not be useful alone for the evaluation of health risks from MW of mobile communication. How the role of other exposure parameters such as frequency, modulation, polarization, duration, and intermittence of exposure should be taken into account is an urgent question to solve. Solving this question would greatly benefit from the knowledge of the physical mechanisms of the NT MW effects.

So far, most laboratory and epidemiological studies did not control important features of the NT MW effects as described above and therefore, only limited conclusion regarding health effects of MW from mobile communication can be drawn from these studies. It should be noted that one group of epidemiologists with a long-lasting experience in studying relationship between mobile phone usage and cancer risk have consistently been concerned regarding importance of various MW signals and exposure durations[19, 150-152]. The group of Hardell was the first epidemiologic group in attempting to study separately the MW signals from cordless phones, analogue phones and digital phones. As a rule, analogue phones had the highest association with the cancer risk. Cordless phones were associated with the risk for brain tumors, acoustic neuroma, and

T-cell lymphoma stronger or in the same degree as digital and analogue phones despite significantly lower SAR values were produced by cordless phones[17, 19, 151, 152]. It should be also noted that epidemiological data are controversial and methodological differences are a subject of debates between various research groups[17, 153]. However, the approach of Hardell's group is more valid from the mechanistic point of view and this should be taken into account when comparing with results of other groups that ignore or minimize the complex dependencies of the NT MW effects on several parameters/variables.

The data about the effects of MW at super low intensities and significant role of duration of exposure in these effects along with the data showing that adverse effects of NT MW from GSM/UMTS mobile phones depend on carrier frequency and type of the MW signal suggest that MW from base-stations/masts can also produce adverse effects at prolonged durations of exposure and encourage the mechanistic *in vitro* studies using real signals from base stations/masts. Further investigations with human primary cells under well controlled conditions of exposure, including all important parameters as described above, are urgently needed to elucidate possible adverse effects of MW signals that are currently being used in wireless communication, especially in new technologies such as UMTS mobile telephony.

The dependence of adverse effects of NT MW from GSM/UMTS mobile phones on carrier frequency and type of signal should be taken into account in settings of safety standards and in planning of *in vivo* and epidemiological studies. Of note, the data from epidemiological studies should be treated with care. Indeed, it is almost impossible to select control unexposed groups because the whole population in many countries is exposed to wide range of MW signals from various sources such as mobile phones and base stations/masts of various kinds, WLAN, WPAN, DECT wireless phones and given that duration of exposure (must be at least 10 years for cancer latency period) may be more important for the adverse health effects of NT MW than PD/SAR. From this point of view, current epidemiological studies may be either inconclusive, if results are negative, or may underestimate the hazard of MW exposure, if results are positive.

The joined efforts of scientific groups within national or international programs are needed for mechanistic studies of the NT MW effects. In order to take unto account all necessary physical parameters and biological variables, these programs should involve scientists with long-lasting experience in studying NT MW effects.

Because NT MW affect not only brain cells, but also blood cells[38-40, 75], skin and fibroblasts[68, 69, 134, 154], stem cells[67, 116, 155], reproductive organs and sperm quality[156-159] the using of hands-free cannot minimize all adverse health effects. Possibilities to minimize the adverse effects of NT MW using various biophysical and biochemical approaches should be studied.

Identification of those signals and frequency channels/bands for mobile communication, which do not affect human cells, is needed as a high priority task for the development of safe mobile communication.

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