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REVIEW ARTICLE

Oxidative mechanisms of biological activity of low-intensity radiofrequency radiation

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ABSTRACT

This review aims to cover experimental data on oxidative effects of low-intensity radiofrequency radiation (RFR) in living cells. Analysis of the currently available peer-reviewed scientific literature reveals molecular effects induced by low-intensity RFR in living cells; this includes significant activation of key pathways generating reactive oxygen species (ROS), activation of peroxidation, **oxidative damage of DNA and changes in the activity of antioxidant enzymes. It indicates that among 100 currently available peer-reviewed studies dealing with oxidative effects of low-intensity RFR, in general, 93 confirmed that RFR induces oxidative effects in biological systems.** A wide pathogenic potential of the induced ROS and their involvement in cell signaling pathways **explains a range of biological/health effects of low-intensity RFR, which include both cancer and non-cancer pathologies**. In conclusion, our analysis demonstrates that low-intensity RFR is an expressive oxidative agent for living cells with a high pathogenic potential and that **the oxidative stress induced by RFR exposure should be recognized as one of the primary mechanisms of the biological activity of this kind of radiation.**

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Introduction

Intensive development of wireless technologies during the last decades led to a dramatic increase of background radiofrequency radiation (RFR) in the human environment. Thus, the level of indoor background RFR in industrialized countries increased 5,000-fold from 1985 to 2005 (Maes, 2005). Such significant environmental changes may have a serious impact on human biology and health. As a proof of such impact, a series of epidemiological studies on the increased risk of tumorigenesis in "heavy" users of wireless telephony exists (Hardell et al., 2007, 2011; Sadetzki et al., 2008; Sato et al., 2011). Some studies indicate that long-term RFR exposure in humans can cause various non-cancer disorders, e.g., headache, fatigue, depression, tinnitus, skin irritation, hormonal disorders and other conditions (Abdel-Rassoul et al., 2007; Buchner & Eger, 2011; Chu et al., 2011; Johansson, 2006; Santini et al., 2002; Yakymenko et al., 2011). In addition, convincing studies on hazardous effects of RFR in human germ cells have been published (Agarwal et al., 2009; De Iuliis et al., 2009).

All abovementioned studies dealt with the effects of low-intensity RFR. This means that the intensity of radiation was far below observable thermal effects in biological tissues, and far below safety limits of the International Commissions on Non-Ionizing Radiation Protection (ICNIRP) (ICNIRP, 1998). To date, molecular mechanisms of non-thermal effects of RFR are still a bottleneck in the research on the biological/health effects of low-intensity RFR, although recently many studies have been carried out on metabolic changes in living cells under low-intensity RFR, and comprehensive reviews were published (Belyaev, 2010; Consales et al., 2012; Desai et al., 2009; Yakymenko et al., 2011). In the present work, we analyze the results of molecular effects of low-intensity RFR in living cells and model systems, with a special emphasis on oxidative effects and free radical mechanisms. It might seem paradoxical that, despite being non-ionizing, RFR can induce significant activation of free radical processes and overproduction of reactive oxygen species (ROS) in living cells. We believe that the analysis of recent findings will allow recognition of a

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general picture of the potential health effects of already ubiquitous and ever-increasing RFR.

Radiofrequency radiation

RFR is a part of electromagnetic spectrum with frequencies from 30 kHz to 300 GHz. RFR is classified as non-ionizing, which means that it does not carry sufficient energy for ionization of atoms and molecules. A part of RFR with the highest frequencies (300 MHz to 300 GHz) is referred to as microwaves (MWs). MW is RFR with the highest energy, which can potentially generate the highest thermal effects in the absorbing matter.

The main indexes of RFR are (i) frequency (Hz); (ii) intensity or power density (PD) of radiation (W/m^2 or $\mu W/cm^2$); (iii) its modulated or non-modulated nature; and (iv) continuous or discontinuous pattern of radiation. For the absorbed RFR energy, a parameter of specific absorption rate (SAR) is used (W/kg). The most common digital standard of RFR for mobile communication is still GSM (Global System for Mobile communication), which utilizes frequencies at about 850, 900, 1800 and 1900 MHz. This radiation is frequency modulated, with channel rotation frequency of 217 Hz, and belongs to the radiation of the pulsed mode (Hyland, 2000).

As to the international safety limits, the ICNIRP recommendations restrict intensity of RFR to 450–1000 $\mu W/cm^2$ (depending on the frequency of radiation) and the SAR value to 2 W/kg, as calculated for human heads and torsos (ICNIRP, 1998). These indexes were adopted by ICNIRP based on the behavioral response of laboratory rats, which were exposed to gradually increased intensities of RFR to determine the point at which the animals became thermally distressed (Gandhi et al., 2012).

Low-intensity RFR is referred to as radiation with intensities which do not induce significant thermal effects in biological tissues. Accordingly, any intensity of RFR under the ICNIRP limits can be referred to as low-intensity. In this paper we will analyze only the effects of low-intensity RFR.

Physical/biophysical effects of low-intensity RFR in living cells

RFR, especially MW, can produce thermal effects in matter due to interaction with charged particles, including free electrons, ions or polar molecules, inducing their oscillations in electromagnetic field. The thermal effect of MW can be seen when warming food in the microwave. The effect strongly depends on the intensity of radiation and is mostly negligible under low-intensity RFR conditions. On the other hand, energy of RFR/MW is insufficient not only for the ionization of molecules, but even for activation of orbital electrons. Hence, RFR was often assessed as a factor producing only thermal effects. Nevertheless, evident biological effects of low-intensity RFR promoted research on physical mechanisms of non-thermal biological effects of this kind of radiation.

A biophysical model of a forced-vibration of free ions on the surface of a cell membrane due to external oscillating electromagnetic field (EMF) was proposed (Panagopoulos et al., 2000, 2002). According to the authors, this vibration of electric charges can cause disruption of the cellular electrochemical balance and functions.

A "moving charge interaction" model was proposed for low-frequency EMF (Blank and Soo, 2001). The authors explained activation of genes and synthesis of stress proteins under EMF exposure due to interaction of the field with moving electrons in DNA (Blank and Soo, 2001; Goodman and Blank, 2002). They also demonstrated that EMF increased electron transfer rates in cytochrome oxidase and accelerated charges in the Na,K-ATPase reaction. Moreover, they demonstrated acceleration of the oscillating Belousov–Zhabotinski reaction in homogeneous solutions due to the application of low-frequency EMF (Blank and Soo, 2003).

An ability of low-strength magnetic fields to trigger onset- and offset-evoked potentials was demonstrated (Marino et al., 2009). Effectiveness of a rapid magnetic stimulus (0.2 ms) has led the authors to a conclusion on direct interaction between the field and ion channels in plasma membrane. A plausible mechanism of overproduction of free radicals in living cell due to electron spin flipping in confined free radical pairs in magnetic field of RFR was proposed (Georgiou, 2010).

A significant effect of low-intensity RFR on ferritin, an iron cage protein present in most living organisms from bacteria to humans, was revealed (Céspedes and Ueno, 2009). Exposure of ferritin solution to low-intensity RFR significantly, up to threefold, reduced iron chelation with ferrozine. The authors explained that magnetic field of RFR plays a principle role in the observed effect, and that this effect is strongly non-thermal. The non-thermal mechanism of the interaction of RFR magnetic fields with ferritin is supposedly mediated by an inner super-paramagnetic nanoparticle ($9H_2O \times 5Fe_2O_3$ with up to 4500 iron ions), which is a natural phenomenon intrinsic to the cells. It results in reduction of input of iron chelates into the ferritin cage. The authors underlined the potential role of ferritin

malfunction for oxidative processes in living cell due to the participation of Fe^{2+} ions in the Fenton reaction, which produces hydroxyl radicals. In this respect, it is interesting to point to the results of an *in vitro* study with RFR exposure of rat lymphocytes treated by iron ions (Zmyślony et al., 2004). Although RFR exposure (930 MHz) did not induce detectable intracellular ROS overproduction, the same exposure in the presence of $FeCl_2$ in the lymphocyte suspensions induced a significant overproduction of ROS.

Another set of studies indicates on a possibility of changes in protein conformation under RFR exposure. Thus, low-intensity 2.45 MHz RFR accelerated conformational changes in β-lactoglobulin through excitation of so-called collective intrinsic modes in the protein (Bohr and Bohr, 2000a, 2000b), which suggests a principal ability of RFR to modulate the non-random collective movements of entire protein domains. Similarly, a frequency-dependent effect on intrinsic flexibility in insulin structure due to applied oscillating electric field was demonstrated (Budi et al., 2007). Moreover, macromolecular structure of cytoskeleton was significantly altered in fibroblasts of Chinese hamster after the exposure to modulated RFR of the GSM standard (Pavicic and Trosic, 2010). Thus, a 3 h exposure of fibroblasts to modulated RFR (975 MHz) led to significant changes in the structure of microtubules and actin microfilaments, which have polar cytoskeleton structures, while non-polar vimentin filaments reportedly stayed unchanged. Taking into account an extensive regulatory potential of cytoskeleton on cell homeostasis, these data could obviously add to the nature of the biological effects of RFR.

It was shown that ornithine decarboxylase (ODC) can significantly change its activity under low-intensity RFR exposure (Byus et al., 1988; Hoyto et al., 2007; Litovitz et al., 1993, 1997; Paulraj et al., 1999).

In addition, so-called "calcium effects" under RFR exposure in living cells have been demonstrated (Dutta et al., 1989; Paulraj et al., 1999; Rao et al., 2008), which include a significant increase in intracellular Ca^{2+} spiking. Taking into account that calcium is a ubiquitous regulator of cellular metabolism, these data point to a possibility that non-thermal RFR can activate multiple Ca^{2+}-dependent signaling cascades.

Finally, an ability of low-intensity MW to dissociate water molecules was demonstrated in model experiments years ago (Vaks et al., 1994). In these experiments, MW of 10 GHz with radiated power 30 mW produced a significant level of H_2O_2 in deionized water (and also in $MgSO_4$ solution) under stable temperature conditions. According to the authors, a kinetic excitation of liquid water associates $C(H_2O)$ upon the absorption of MW leads to subsequent viscous losses due to friction between moving clusters of water molecules. It results in partial irreversible decomposition of water, including breaks of intramolecular bonds (H–OH) due to a mechanochemical reaction, and generation of $H^{\bullet}$; $OH^{\bullet}$; H^{+} and OH^{-} groups. Among these, the hydroxyl radical ($OH^{\bullet}$) is the most aggressive form of ROS, which can break any chemical bond in surrounding molecules (Halliwell, 2007). The authors assessed that this type of mechanochemical transformation in water could be responsible for 10^{-4}–10^{-8} relative parts of the total MW energy absorbed. Given the fact that the water molecules are ubiquitous in living cells, even a subtle chance for dissociation of water molecules under low-intensity RFR exposure could have a profound effect on tissue homeostasis. It is of note here that one $OH^{\bullet}$ radical can initiate irreversible peroxidation of many hundreds of macromolecules, e.g. lipid molecules (Halliwell, 1991). Taken together, these data show that non-thermal RFR can be absorbed by particular charges, molecules and cellular structures, and in this way can potentially induce substantial modulatory effects in living cell.

Generation of reactive oxygen species under RFR exposure in living cells

NADH oxidase of cellular membrane was suggested as a primary mediator of RFR interaction with living cells (Friedman et al., 2007). Using purified membranes from HeLa cells, the authors experimentally proved that the exposure to RFR of 875 MHz, 200 μW/cm^2 for 5 or 10 min significantly, almost threefold, increased the activity of NADH oxidase. NADH oxidases are membrane-associated enzymes that catalyze one-electron reduction of oxygen into superoxide radical using NADH as a donor of electron, thus producing powerful ROS. This enzyme has been traditionally known due to its role in induction of oxidative burst in phagocytes as a part of immune response. Yet, later the existence of non-phagocytic NAD(P)H oxidases was revealed in various types of cells, including fibroblasts, vascular and cardiac cells (Griendling et al., 2000). Obviously, the presence of superoxide-generating enzyme in many types of non-phagocytic cells points to the considerable regulatory roles of ROS in living cells. On the other hand, an ability of low-intensity RFR to modulate the activity of the NADH oxidase automatically makes this factor a notable and potentially dangerous effector of cell metabolism. Notably, the authors pointed out that the acceptor of RFR is different from the peroxide-generating NADPH oxidases, which are also found in plasma membranes (Low et al., 2012).

The other powerful source of ROS in cells is mitochondrial electron transport chain (ETC), which can generate superoxide due to breakdowns in electron transport (Inoue et al., 2003). It was demonstrated that generation of ROS by mitochondrial pathway can be activated under RFR exposure in human spermatozoa (De Iuliis et al., 2009). The authors revealed a dose-dependent effect of 1.8 GHz RFR exposure on ROS production in spermatozoa, particularly in their mitochondria. The significantly increased level of total ROS in spermatozoa was detected under RFR with SAR = 1 W/kg, which is below the safety limits accepted in many countries. It was demonstrated recently in our laboratory that the exposure of quail embryos *in ovo* to extremely low-intensity RFR (GSM 900 MHz, 0.25 μW/cm^2) during the initial days of embryogenesis resulted in a robust overproduction of superoxide and nitrogen oxide radicals in mitochondria of embryonic cells (Burlaka et al., 2013). It is not clear yet which particular part of ETC is responsible for the interaction with RFR. To date, three possible sites of generation of superoxide in ETC have been shown: the ETC complex I (Inoue et al., 2003), complex II (Liu et al., 2002), and complex III (Guzy and Schumacker, 2006). A significant inverse correlation between mitochondrial membrane potential and ROS levels in living cell was found (Wang et al., 2003). As the authors underlined, such a relationship could be due to two mutually interconnected phenomena: ROS causing damage to the mitochondrial membrane, and the damaged mitochondrial membrane causing increased ROS production.

In addition to the well-established role of the mitochondria in energy metabolism, regulation of cell death is a second major function of these organelles. This, in turn, is linked to their role as the powerful intracellular source of ROS. Mitochondria-generated ROS play an important role in the release of cytochrome c and other pro-apoptotic proteins, which can trigger caspase activation and apoptosis (Ott et al., 2007). A few reports indicate on activation of apoptosis due to low-intensity RFR exposure. In human epidermoid cancer KB cells, 1950 MHz RFR induced time-dependent apoptosis (45% after 3 h) that is paralleled by 2.5-fold decrease of the expression of ras and Raf-1 and of the activity of ras and Erk-1/2 (Caraglia et al., 2005). Primary cultured neurons and astrocytes exposed to GSM 1900 MHz RFR for 2 h demonstrated up-regulation of caspase-2, caspase-6 and Asc (apoptosis associated speck-like protein containing a card) (Zhao et al., 2007). Up-regulation in neurons occurred in both "on" and "stand-by" modes, but in astrocytes only in the "on" mode. We should underline that, in that study an extremely high biological sensitivity to RFR was demonstrated, as a cell phone in the "stand-by" position emits negligibly low-intensity of radiation (up to hundredths μW/cm^2).

Based on the analysis of available literature data, we identified altogether 100 experimental studies in biological models which investigated oxidative stress due to low-intensity RFR exposures. From these 100 articles, 93 studies (93%) demonstrated significant oxidative effects induced by low-intensity RFR exposure (Table 1–3), while 7 studies (7%) demonstrated the absence of significant changes (Table 4). The total number includes 18 *in vitro* studies, 73 studies in animals, 3 studies in plants and 6 studies in humans. Majority of the research was done on laboratory rats (58 studies, with 54 positive results), while 4 studies out of 6 in humans were positive. From the *in vitro* studies, 17 were positive (94.4%), including 2 studies on human spermatozoa and 2 studies on human blood cells.

Most of the studies utilized RFR exposure in MW range, including a use of commercial or trial cell phones as sources of radiation. The power densities of RFR applied in positive studies varied from 0.1 μW/cm^2 (Oksay et al., 2014) to 680 μW/cm^2 (Jelodar et al., 2013) and SAR values varied from 3 μW/kg (Burlaka et al., 2013) to the ICNIRP recommended limit of 2 W/kg (Naziroglu et al., 2012a; Xu et al., 2010). Exposure times in positive studies varied from 5 min (Friedman et al., 2007) to 12.5 years, 29.6 h/month (Hamzany et al., 2013).

The most often used indexes of oxidative stress analyzed in the studies were ROS production, levels of lipid peroxidation (LPO)/malondialdehyde (MDA), protein oxidation (PO), nitric oxides (NO_x), glutathione (GSH), activity of antioxidant enzymes (superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px)). It is important that some studies directly pointed to induction of free radicals (superoxide radical, NO) as a primary reaction of living cells to RFR exposure (Burlaka et al., 2013; Friedman et al., 2007). As we pointed out earlier, direct activation of NADH oxidase (Friedman et al., 2007) and the mitochondrial pathway of superoxide overproduction (Burlaka et al., 2013; De Iuliis et al., 2009) have been experimentally proven. Besides, a significant overproduction of nitrogen oxide was revealed in some studies (Avci et al., 2012; Bilgici et al., 2013; Burlaka et al., 2013), although it is unclear whether an induction of expression of NO-synthases or direct activation of the enzyme took place. It is however clear that significantly increased levels of these free radical species (superoxide and nitrogen oxide) in cells due to RFR exposure result in an activation of peroxidation and repression of activities of key antioxidant enzymes. It is indicative that many studies demonstrated effectiveness of different

Table 1. Publications which reported positive findings on oxidative stress caused by RFR exposure of cells *in vitro*.

Reference	Biological system exposed	RFR exposure	Statistically significant effects reported*
(Agarwal et al., 2009)	Human spermatozoa	Cell phone RFR, in talk mode, for 1 h	Increase in reactive oxygen species (ROS) level, decrease in sperm motility and viability.
(Campisi et al., 2010)	Rat astroglial cells	900 MHz (continuous or modulated), electric field 10 V/m, for5; 10; 20 min	Increase in ROS levels and DNA fragmentation after exposure to modulated RFR for 20 min.
(De Iuliis et al., 2009)	Human spermatozoa	1.8 GHz, SAR = 0.4–27.5 W/kg	Increased amounts of ROS.
(Friedman et al., 2007)	HeLa membranes	875 MHz, 200 μW/cm^2, for 5 and 10 min	Increased NADH oxidase activity.
(Hou et al., 2014)	Mouse embryonic fibroblasts (NIH/3T3)	1800-MHz GSM-talk mode RFR, SAR = 2 W/kg, intermittent exposure (5 min on/ 10 min off) for 0.5–8 h	Increased intracellular ROS levels.
(Kahya et al., 2014)	Cancer cell cultures	900 MHz RFR, SAR = 0.36 W/kg, for 1 h	Induced apoptosis effects through oxidative stress, selenium counteracted the effects of RFR exposure.
(Lantow et al., 2006a)	Human blood cells	Continuous wave or GSM signal,SAR = 2 W/kg, for 30 or 45 min of continuous or 5 min ON, 5 min OFF	After continuous or intermittent GSMsignal a different ROS production was detected in human monocytes compared to sham.
(Lantow et al., 2006b)	Human Mono Mac 6 and K562 cells	Continuous wave, GSM speaking only, GSM hearing only, GSM talk, SARs of 0.5, 1.0, 1.5 and 2.0 W/kg.	The GSM-DTX signal at 2 W/kg produced difference in free radical production compared to sham.
(Liu et al., 2013b)	GC-2 cells	1800 MHz, SAR = 1; 2 W/kg,5 min ON, 10 min OFF for 24 h	In the 2 W/kg exposed cultures, the level of ROS was increased.
(Lu et al., 2012)	Human blood mononuclear cells	900 MHz, SAR = 0.4 W/kg, for 1–8 h	The increased level of apoptosis induced through the mitochondrial pathway and mediated by activating ROS and caspase-3.
(Marjanovic et al., 2014)	V79 cells	1800 MHz, SAR = 1.6 W/kg, for 10, 30 and 60 min	ROS level increased after 10 min of exposure. Decrease in ROS level after 30-min treatment indicating antioxidant defense mechanism activation.
(Naziroglu et al., 2012b)	HL-60 cells	2450 MHz, pulsed, SAR = 0.1–2.5 W/kg, for 1; 2; 12 or 24 h	Lipid peroxide (LPO) levels were increased at all exposure times.
(Ni et al., 2013)	Human lens epithelial cells	1800 MHz, SAR = 2; 3; 4 W/kg	The ROS and malondialdehyde (MDA) levels were increased.
(Pilla, 2012)	Neuronal cells and human fibroblasts	27.12 MHz, pulsed, electric field 41 V/m, 2 min prior to lipopolysaccharide administration or for 15 min	Increased level of nitric oxide (NO).
(Sefidbakht et al., 2014)	HEK293T cells	940 MHz, SAR = 0.09 W/kg, for 15, 30, 45, 60 and 90 min	ROS generation increased in the 30 min exposed cells. A sharp rise in catalase (CAT) and superoxide dismutase (SOD) activity and elevation of glutathione (GSH) during the 45 min exposure.
(Xu et al., 2010)	Primary cultured neurons	1800 MHz, pulsed, SAR = 2 W/kg, for 24 h	An increase in the levels of8-hydroxy-2'-deoxyguanosine (8-OH-dG).
(Zmyślony et al., 2004)	Rat lymphocytes	930 MHz, PD of 500 μW/cm^2, SAR = 1.5 W/kg, for 5 and 15 min	Intracellular ROS level increased in exposed $FeCl_2$ treated cells compared with unexposed $FeCl_2$ treated cells.

*All effects were statistically significant (at least $p < 0.05$) as compared to control or sham exposed groups.

antioxidants to override oxidative stress caused by RFR exposure. Such effects have been reported for melatonin (Ayata et al., 2004; Lai and Singh, 1997; Oktem et al., 2005; Ozguner et al., 2006; Sokolovic et al., 2008), vitamin E and C (Jelodar et al., 2013; Oral et al., 2006), caffeic acid phenethyl ester (Ozguner et al., 2006), selenium, L-carnitine (Turker et al., 2011) and garlic (Avci et al., 2012; Bilgici et al., 2013).

It is worthwhile to emphasize a strict non-thermal character of ROS overproduction under RFR exposure described in the cited reports. As low as 0.1 μW/cm^2 intensity of RFR and absorbed energy (specific absorption rate, SAR) of 0.3 μW/kg were demonstrated to be effective in inducing significant oxidative stress in living cells (Burlaka et al., 2013; Oksay et al., 2014). This observation is particularly important as the modern international safety limits on RFR exposure are based solely on the thermal effects of radiation and only restrict RFR intensity to 450–1000 μW/cm^2 and SAR to 2 W/kg (ICNIRP, 1998). Moreover, studies where high (thermal) intensities of RFR have been used could not reveal oxidative effects (Hong et al., 2012; Kang et al., 2013; Luukkonen et al., 2009), which might point to the variety of molecular mechanisms for different radiation intensities.

Taken together, the analysis of the contemporary scientific literature on the biological effects of RFR persuasively proves that the exposure to low-intensity RFR in living cells leads to generation of significant levels of ROS and results in a significant oxidative stress.

Oxidative damage of DNA under RFR exposure

To date more than hundred papers have been published on mutagenic effects of RFR and most of them revealed significant effects (Ruediger, 2009). There is a substantial number of studies which demonstrated the formation of micronuclei (Garaj-Vrhovac et al., 1992; Tice et al., 2002; Zotti-Martelli et al., 2005) or structural anomalies of metaphase chromosomes (Garson et al., 1991; Kerbacher et al., 1990; Maes et al., 2000) in living

Table 2. Publications which reported positive findings on oxidative stress caused by RFR exposure of animals and plants.

Reference	Biological system exposed	RFR exposure	Statistically significant effects reported*
(Akbari et al., 2014)	Rat whole body	RFR from base transceiver station	Glutathione peroxidase (GSH-Px), SOD, and CAT activity decreased and level of MDA increased. Vitamin C reduced the effect.
(Al-Damegh, 2012)	Rat whole body	Cell phone RFR, 15, 30, or 60 min/day for 2 weeks	Levels of conjugated dienes, LPO and CAT activities in serum and testicular tissue increased, the total serum and testicular tissue GSH and GSH-Px levels decreased.
(Avci et al., 2012)	Rat whole body	1800 MHz, SAR = 0.4 W/kg, 1 h/day for 3 weeks	An increased level of protein oxidation (PO) in brain tissue and an increase in serum NO. Garlic administration reduced protein oxidation in brain tissue.
(Ayata et al., 2004)	Rat whole body	900 MHz, 30 min/day for 10 days	MDA and hydroxyproline levels and activities of CAT and GSH-Px were increased, andsuperoxide dismutase (SOD) activity was decreased in skin. Melatonin treatment reversed effect.
(Aynali et al., 2013)	Rat whole body	2450 MHz, pulsed, SAR = 0.143 W/kg,60 min/day for 30 days	LPO was increased, an administration of melatonin prevented this effect.
(Balci et al., 2007)	Rat whole body	"Standardized daily dose" of cell phoneRFR for 4 weeks	In corneal tissue, MDA level and CAT activity increased, whereas SOD activity was decreased. In the lens tissues, the MDA level was increased.
(Bilgici et al., 2013)	Rat whole body	850–950 MHz,SAR = 1.08 W/kg,1 h/day for 3 weeks	The serum NO levels and levels of MDA and the PO in brain were increased. An administration of garlic extract diminished these effects.
(Bodera et al., 2013)	Rat whole body	1800 MHz, GSM, for 15 min	Reduced antioxidant capacity both in healthy animals and in those with paw inflammation.
(Burlaka et al., 2013)	Quail embryo *in ovo*	GSM 900 MHz, power density (PD) of 0.25 μW/cm^2, SAR = 3 μW/kg, 48 sec ON - 12 sec OFF, for 158–360 h	Overproduction of superoxide and NO, increased levels of thiobarbituric acid reactive substances (TBARS) and 8-OH-dG, decreased SOD and CAT activities.
(Burlaka et al., 2014)	Male rat whole body	Pulsed and continuous MWin the doses equivalent to the maximal permitted energy load for the staffs of the radar stations	Increased rates of superoxide production, formation of the iron-nitrosyl complexes and decreased activity of NADH-ubiquinone oxidoreductase complex in liver, cardiac and aorta tissues 28 days after the exposure.
(Cenesiz et al., 2011)	Guinea pig whole body	900; 1800 MHz RFR from base station antennas, 4 h/day for 20 days	Difference in guinea pigs subjected to 900 and 1800 MHz for plasma oxidant status levels. NO level changed in 900 MHz subjected guinea pigs, as compared to the control.
(Cetin et al., 2014)	Pregnant rats and offspring	900; 1800 MHz RFR, 1 h/day during pregnancy and neonatal development	Brain and liver GSH-Px activities, selenium concentrations in the brain and liver vitamin A and β-carotene concentrations decreased in offspring.
(Dasdag et al., 2009)	Head of rats	900 MHz, 2 h/day for 10 months	The total antioxidant capacity and CATactivity in brains were higher than that in the sham group.
(Dasdag et al., 2012)	Head of rats	900 MHz, cell-phones-like, 2 h/day for 10 months	Protein carbonyl level was higher in the brain of exposedrats.
(Dasdag et al., 2008)	Rat whole body	900 MHz, PD of 78 μW/cm^2, 2 h/days for10 months.	Increased levels of MDA and total oxidative status in liver tissue.
(Deshmukh et al., 2013)	Rat whole body	900 MHz, 2 h/day, 5 days a week for 30 days	The levels of LPO and PO were increased.
(Esmekaya et al., 2011)	Rat whole body	900 MHz, pulsed, modulated, SAR = 1.2 W/kg, 20 min/day for 3 weeks	The increased level of MDA and NOx, and decreased levels of GSH in liver, lung, testis and heart tissues.
(Furtado-Filho et al., 2014)	Rat whole body	950 MHz, SAR = 0.01–0.88 W/kg,30 min/day for 21 days during pregnancy (or additionally 6 or 15 days of postnatal period)	Neonatal rats exposed in utero had decreased levels of CAT and lower LPO, and genotoxic effect.
(Guler et al., 2012)	Rabbit infant whole body	GSM 1800 MHz, 15 min/day for 7 days (females) or 14 days (males)	LPO levels in the liver tissues of females and males increased,liver 8-OH-dG levels of females were increased.
(Guney et al., 2007)	Rat whole body	900 MHz, 30 min/day for 30 days	Endometrial levels of NO and MDA increased, endometrial SOD, CAT and GSH-Px activities were decreased.Vitamin E and C treatment prevented these effects.
(Gürler et al., 2014)	Rat whole body	2450 MHz, 3.68 V/m, 1 h/day for 30 days	Increased 8-OH-dG level in both plasma and brain tissue whereas it increased PO level only in plasma. Garlic prevented the increase of 8-OH-dG level in brain tissue and plasma PO levels.
(Ilhan et al., 2004)	Rat whole body	900 MHz, from cell phone,1 h/day for 7 days	Increase in MDA, NO levels, andxanthine oxidase (XO) activity, decrease in SOD and GSH-Px activities in brain. These effects were prevented by Ginkgo bilobaextract treatment.
(Jelodar, et al., 2013)	Rat whole body	900 MHz, PD of 680 μW/cm^2, 4 h/day for 45 days,	The concentration of MDA was increased and activities of SOD, GSH-Px and CAT were decreased in rat eyes. An administration of vitamin C prevented these effects.
(Jelodar et al., 2013)	Rat whole body	900 MHz, daily for 45 days	Increased level of MDA and decreased antioxidant enzymes activity in rat testis.
(Jing et al., 2012)	Rat whole body	Cell phone RFR, SAR = 0.9 W/kg,3 x 10; 30 or 60 min for 20 days during gestation	After 30 and 60 min the level of MDA was increased, the activities of SOD and GSH-Pxwere decreased.

(*Continued*)

Table 2. (Continued).

Reference	Biological system exposed	RFR exposure	Statistically significant effects reported*
(Kerman & Senol, 2012)	Rat whole body	900 MHz, 30 min/day for 10 days	Tissue MDA levels were increased, SOD, CAT and GSH-Pxactivities were reduced. Melatonin treatment reversed these effects.
(Kesari et al., 2010)	Male rat whole body	Cell phone RFR, SAR = 0.9 W/kg,2 h/day for 35 days	Reduction in protein kinase activity, decrease in sperm count and increase in apoptosis.
(Kesari et al., 2011)	Rat whole body	900 MHz, pulsed, SAR = 0.9 W/kg,2 h/day for 45 days	Increase in the level of ROS, decrease in the activities of SOD and GSH-Px,and in the level of pineal melatonin.
(Kesari et al., 2013)	Rat whole body	2115 MHz, SAR = 0.26 W/kg,2 h/day for 60 days	The level of ROS, DNA damage and theapoptosis rate were increased.
(Khalil et al., 2012)	Rat whole body	1800 MHz, electric field 15–20 V/m, for2 h	Elevations in the levels of 8-OH-dG in urine.
(Kismali et al., 2012)	Rabbit whole body (non-pregnant and pregnant)	1800 MHz, GSM modulation, 15 min/day for 7 days	Creatine kinases levels' changes.
(Koc et al., 2013)	Male rat whole body	Cell phone RFR at calling or stand-by	Oxidative stress detected at both calling and stand-by exposures.
(Koylu et al., 2006)	Rat whole body	900 MHz	The levels of LPO in the brain cortex and hippocampus increased.These levels in the hippocampus were decreased by melatonin administration.
(Koyu et al., 2009)	Rat whole body	900 MHz	The activities of XO, CAT and level of LPO increased in liver.XO, CAT activities and LPO levels were decreased by caffeic acid phenethyl ester (CAPE) administration.
(Kumar et al., 2014)	Rat whole body	Cell phone 1910.5 MHz RFR, 2 h/day for 60 days day (6 days a week).	Increase in LPO, damage in sperm cells and DNA damage.
(Lai & Singh, 1997)	Rat whole body	2450 MHz, pulsed, PD = 2 mW/cm^2, SAR = 1.2 W/kg	Melatonin or spin-trap compound blocked DNA strand breaks induced by RFR exposure in rat brain cells.
(Luo et al., 2014)	Rat whole body	900 MHz imitated cell phone RFR, 4 h/day for 12 days	Contents of liver MDA and Nrf2 protein increased, contents of liver SOD and GSH decreased.
(Mailankot et al., 2009)	Rat whole body	900/1800 MHz,GSM,1 h/day for 28 days	Increase in LPO and decreased GSH content in the testis and epididymis.
(Manta et al., 2013)	Drosophila whole body	1880–1900 MHz, DECT modulation, SAR = 0.009 W/kg, for 0.5–96 h	Increase in ROS levels in male and female bodies, a quick response in ROS increase in ovaries.
(Marzook et al., 2014)	Rat whole body	900 MHz from cellular tower, 24 h/day for 8 weeks	SOD and CAT activities were reduced in blood, sesame oil reversed the effect
(Meena et al., 2013)	Rat whole body	2450 MHz, PDof 210 μW/cm^2, SAR = 0.14 W/kg, 2 h/day for 45 days	Increased level of MDA and ROS in testis. Melatonin prevented oxidative stress.
(Megha et al., 2012)	Rat whole body	900; 1800 MHz, PD of 170 μW/cm^2, SAR = 0.6 mW/kg, 2 h/day, 5 days/week for 30 days	The levels of the LPO and PO were increased; the level of GSH was decreased.
(Meral et al., 2007)	Guinea pig whole body	890–915 MHz,from cell phone, SAR = 0.95 w/kg, 12 h/day for 30 days (11 h 45 min stand-by and 15 min spiking mode)	MDA level increased, GSH level and CAT activity weredecreased in the brain. MDA, vitamins A, D_3 and E levels and CAT enzyme activity increased, and GSH level was decreased in the blood.
(Motawi et al., 2014)	Rat whole body	Test cellphone RFR, SAR = 1.13 W/kg, 2 h/day for 60 days	Increments in conjugated dienes, protein carbonyls, total oxidant status and oxidative stress index along with a reduction of total antioxidant capacity levels.
(Naziroglu & Gumral, 2009)	Rat whole body	2450 MHz,60 min/day for 28 days	Decrease of the cortex brain vitamin A, vitamin C and vitamin E levels.
(Naziroglu et al., 2012a)	Rat whole body	2450 MHz, 60 min/day for 30 days	LPO, cell viability and cytosolic Ca^{2+} values in dorsal root ganglion neurons were increased.
(Oksay et al., 2014)	Rat whole body	2450 MHz, pulsed, PD of0.1 μW/cm^2, SAR = 0.1 W/kg, 1 h/day for 30 days	LPO was higher in exposed animals. Melatonin treatment reversed the effect.
(Oktem et al., 2005)	Rat whole body	900 MHz, 30 min/day for 10 days	Renal tissue MDA level increased, SOD, CAT and GSH-Px activities were reduced. Melatonin treatment reversed these effects.
(Oral et al., 2006)	Rat whole body	900 MHz, 30 min/day for 30 days	Increased MDA levels and apoptosis in endometrial tissue.Treatment with vitamins E and C diminished these changes.
(Ozguner et al., 2005a)	Rat whole body	900 MHz, 30 min/day for 10 days	Heart tissue MDA and NO levels increased, SOD, CAT and GSH-Px activities were reduced. CAPE treatment reversed these effects.
(Ozguner et al., 2006)	Rat whole body	900 MHz, from cell phone	Retinal levels of NO and MDA increased, SOD, GSH-Px and CAT activities were decreased.Melatonin and CAPE treatment prevented effects.
(Ozguner et al., 2005b)	Rat whole body	900 MHz	Renal tissue MDA and NO levels increased, the activities of SOD, CAT and GSH-Px were reduced. CAPE treatment reversed these effects.
(Ozgur et al., 2010)	Guinea pig whole body	1800 MHz,GSM, SAR = 0.38 W/kg, 10 or 20 min/day for 7 days	Increases in MDA and total NO(x) levels and decreases in activities of SOD, myeloperoxidase and GSH-Px in liver. Extent of oxidative damage was proportional to the duration of exposure.
(Ozgur et al., 2013)	Rabbit whole body	1800 MHz, pulsed, 15 min/day for 7 days in pregnant animals, for 7 or 15 days in infants	The amount of LPO was increased in the prenatal exposure group.

(*Continued*)

Table 2. (Continued).

Reference	Biological system exposed	RFR exposure	Statistically significant effects reported*
(Özorak et al., 2013)	Rat whole body	900; 1800; 2450 MHz, pulsed, PD of 12 μW/cm^2. SAR = 0.18; 1.2 W/kg, 60 min/day during gestation and 6 weeks following delivery	At the age of six weeks, an increased LPO in the kidney and testis, and decreased level of GSH and total antioxidant status.
(Qin et al., 2014)	Male mouse whole body	1800 MHz, 208 μW/cm^2, 30 or 120 min/d for 30 days	Decreased activities of CAT and GSH-Px and increasedlevel of MDA in cerebrum. Nano-selenium decreased MDA level, and increased GSH-Px and CAT activities.
(Ragy, 2014)	Rat whole body	Cell phone 900 MHz RFR, 1 h/d for 60 days	Increase in MDA levels and decrease total antioxidant capacity levels in brain, liver and kidneys tissues. These alterations were corrected by withdrawal of RFR exposure during 30 days.
(Saikhedkar et al., 2014)	Rat whole body	Cell phone 900 MHz RFR, 4 h/d for 15 days	A significant change in level of antioxidant enzymes and non-enzymatic antioxidants, and an increase in LPO.
(Shahin et al., 2013)	Mouse whole body	2450 MHz, PD of 33.5 μW/cm^2, SAR = 23 mW/kg, 2 h/day for 45 days	An increase in ROS, decrease in NO and antioxidant enzymes activities.
(Sharma et al., 2009)	Plant(mung bean) whole body	900 MHz, from cell phone, PD of 8.55 μW/cm^2; for 0.5; 1; 2, and 4 h	Increased level of MDA,H_2O_2 accumulation and root oxidizability, upregulation in the activities of SOD, CAT, ascorbate peroxidases, guaiacol peroxidases and GSHreductases in roots.
(Singh et al., 2012)	Plant (mung bean) whole body	900 MHz,from cell phone	The increased level of MDA, hydrogen peroxide and proline content in hypocotyls.
(Sokolovic et al., 2008)	Rat whole body	RFR from cell phone, SAR = 0.043–0.135 W/kg, for 20, 40 and 60 days	An increase in the brain tissue MDA and carbonyl group concentration. Decreased activity of CAT and increased activity of xanthine oxidase (XO). Melatonin treatment prevented the effects.
(Sokolovic et al., 2013)	Rat whole body	900 MHz, SAR = 0,043–0.135 W/kg,4 h/day for 29; 40 or 60 days,	The level of LPO and PO, activities of CAT, XO, number of apoptotic cells were increased in thymus tissue. An administration of melatonin prevented these effects.
(Suleyman et al., 2004)	Rat whole body	Cell phoneRFR,SAR = 0.52 W/kg,20 min/day for 1 month	MDA concentration was increased in brains.
(Tkalec et al., 2007)	Plant Lemna minor (duckweed)	400 and 900 MHz, 10, 23, 41 and 120 V/m, for 2 or 4 h	LPO and H_2O_2 content increased: CAT activity increased, pyrogallol peroxidase decreased.
(Tkalec et al., 2013)	Earthworm whole body	900 MHz, PD of 30–3800 μW/cm^2, SAR = 0.13–9.33 mW/kg, for 2 h	The protein carbonyl content was increased in all exposures above 30 μWc/m^2. The level of MDA was increased at 140μW/cm^2.
(Tök et al., 2014)	Rat whole body	2450 MHz, Wi-Fi RFR, 60 min/day for 30 days	Decreased GSH-Px activity. GSH-Px activity and GSH values increased after melatonin treatment.
(Tomruk et al., 2010)	Rabbit whole body	1800 MHz, GSM-like signal, 15 min/day for a week	Increase of MDA and ferrous oxidation in xylenol orange levels.
(Tsybulin et al., 2012)	Quail embryo *in ovo*	900 MHz, fromcell phone, GSM, PD of 0.024–0.21 μW/cm^2, intermittent for 14 days	Increased level of TBARS in brains and livers of hatchlings.
(Turker et al., 2011)	Rat partial body	2450 MHz, pulsed, SAR = 0.1 W/kg,1 h/day for 28 days	The increased level of LPO, the decreased concentrations of vitamin A, vitamin C and vitamin E. There was a protective effect of selenium and L-carnitine.
(Türedi et al., 2014)	Pregnant rat whole body	900 MHz, 13.7 V/m, 50 μW/cm^2, 1 h/day for 13–21 days of pregnancy	MDA, SOD and CAT values increased, GSH values decreased in exposed pups.
(Yurekli et al., 2006)	Rat whole body	945 MHz, GSM, PD of 367 μW/cm^2, SAR = 11.3 mW/kg	MDA level and SOD activity increased, GSH concentration was decreased.

*All effects were statistically significant (at least $p < 0.05$) as compared to control or sham exposed groups.

Table 3. Publications which reported positive findings on oxidative stress caused by RFR exposure of humans.

Reference	Biological system exposed	RFR exposure	Statistically significant effects reported*
(Abu Khadra et al., 2014)	Human male head	GSM 1800 MHz from cell phone, SAR = 1.09 W/kg, for 15 and 30 min	SOD activity in saliva increased.
(Garaj-Vrhovac et al., 2011)	Human whole body	3; 5.5; 9.4 GHz, pulsed, from radars	Increased level of MDA, decreased level of GSH.
(Hamzany et al., 2013)	Human head/ whole body	RFR from cell phone a mean time of 29.6 h/month for 12.5 years	Increase in all salivary oxidative stress indices.
(Moustafa et al., 2001)	Human male body	Cell phone in a pocket in standby position, for 1; 2 or 4 h	Plasma level of LPO was increased, activities of SOD and GSH-Px in erythrocytes decreased.

*All effects were statistically significant (at least $p < 0.05$) as compared to control or sham-exposed groups.

cells due to low-intensity RFR exposure. However, majority of the studies on the mutagenic effects of RFR successfully used a comet assay approach (Baohong et al., 2005; Belyaev et al., 2006; Diem et al., 2005; Kim et al., 2008; Lai and Singh, 1996; Liu et al., 2013a). Particular studies identified specific marker of oxidative damage of DNA, 8-hydroxy-2'-deoxyguanosine (8-OH-dG) (Burlaka et al., 2013; De Iuliis et al.,

Table 4. Publications which reported no significant oxidative effects after RFR exposure.

Reference	Biological system exposed	RFR exposure	Effects reported
(Hook et al., 2004)	Mammalian cells *in vitro*	835.62 MHz (frequency-modulated continuous-wave, FMCW) and 847.74 MHz (code division multiple access, CDMA), SAR = 0.8 W/kg, for 20–22 h	FMCW- and CDMA-modulated RFR did not alter parameters indicative of oxidative stress.
(Ferreira et al., 2006a)	Rat whole body	800–1800 MHz, from cell phone	No changes in lipid and protein damage, and in non-enzymatic antioxidant defense in frontal cortex or hippocampus.
(Ferreira et al., 2006b)	Pregnant rat whole body	RFR from cell phone	No differences in oxidative parameter of offspring blood and liver, but increase in erythrocytes micronuclei incidence in offspring.
(Dasdag et al., 2003)	Rat whole body	Cell phone RFR, SAR = 0.52 W/kg, 20 min/day for 1 month	No alteration in MDA concentration.
(Demirel et al., 2012)	Rat whole body	3G cell phone RFR, "standardized daily dose" for 20 days	No difference in GSH-Px and CAT activity in eye tissues, in MDA and GSH levels in blood.
(Khalil et al., 2014)	Human head/whole body	Cell phone RFR (talking mode) for 15 or 30 min	No relationship between exposure and changes in the salivary oxidant/antioxidant profile.
(de Souza et al., 2014)	Human head/whole body	Cell phone RFR	No difference in the saliva from the parotid gland exposed to cell phone RFR to the saliva from the opposite gland of each individual.

2009; Guler et al., 2012; Khalil et al., 2012; Xu et al., 2010). Thus, the level of 8-OH-dG in human spermatozoa was shown to be significantly increased after *in vitro* exposure to low-intensity RFR (De Iuliis et al., 2009). Likewise, we demonstrated that the exposure of quail embryos *in ovo* to GSM 900 MHz of 0.25 μW/cm^2 during a few days was sufficient for a significant, two-threefold, increase of 8-OH-dG level in embryonic cells (Burlaka et al., 2013).

It would be logical to assume that most mutagenic effects due to the RFR exposure are caused by oxidative damage to DNA, as the overproduction of ROS in living cells due to RFR exposure was reliably documented. It is known that superoxide itself does not affect DNA. The most aggressive form of ROS, which is able to affect the DNA molecule directly, is hydroxyl radical (Halliwell, 2007). The hydroxyl radicals are generated in cell in the Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\bullet} + OH^{-}$) and in the Haber–Weiss reaction ($O_2^{\bullet -} + H_2O_2 \rightarrow O_2 + OH^{\bullet} + OH^{-}$) (Valko et al., 2006). On the other hand, increased concentration of NO in addition to superoxide in the RFR-exposed cells can lead to the formation of other aggressive form of ROS, peroxynitrite ($ONOO^{-}$), which can also cause DNA damage (Valko et al., 2006).

Free radicals induced under the RFR exposure can perturb cellular signaling

Taking into account the abovementioned data, we can state that the exposure to RFR leads to overproduction of free radicals/ROS in living cell. Certainly, free radicals can induce harmful effects via direct damage due to oxidation of biological macromolecules. To that, it becomes clear nowadays that free radicals/ROS are an intrinsic part of the cellular signaling cascades (Forman et al., 2014). Thus, hydrogen peroxide appears as a second messenger both in insulin signaling and in growth factor-induced signalling cascades (Sies, 2014). These species are also implicated in biochemical mechanism of oxidation of ethanol and in other metabolic processes (Oshino et al., 1975) and is also required for initiation of wound repair (Enyedi and Niethammer, 2013). In addition, ROS at relatively low concentrations can modulate inflammation via activation of NF-kB pathway (Hayden and Ghosh, 2011). Therefore, even subtle exposures to RFR with generation of hardly detectable quantities of free radicals can have their meaningful biological consequences.

We could ascertain the signaling effects of moderate levels of free radicals from our experiments in quail embryos irradiated with the commercial cell phone. Thus, we were able to show that the prolonged exposures of embryos *in ovo* led to robust repression of their development (Tsybulin et al., 2013), which was concomitant with significant overproduction of superoxide radical and NO radical, increased rates of lipid peroxidation and oxidative damage of DNA (Burlaka et al., 2013; Tsybulin et al., 2012). Notably, shorter exposures instead led to enhancement in embryonic development (Tsybulin et al., 2012, 2013). We demonstrated the favorable effects of shorter exposures also on the molecular level. Thus, after the short-time RFR exposure the DNA comets in embryonic cells were significantly shorter than in the control non-irradiated embryos, pointing to activation of mechanisms maintaining the integrity of DNA. The "beneficial" consequences of the irradiation could be explained by hormesis effect (Calabrese, 2008). However, one could hypothesize that the "beneficial" effects of the irradiation could be explained by the signaling action of free radicals induced at levels below the damaging concentrations.

Obviously, any seemingly beneficial effect of external environmental impact should be treated with caution and possibly minimized before careful evaluation of the long-term consequences. Altogether, this gives a clear warning of the adverse health effects of low-intensity RFR, which could be evoked both by the direct oxidative damage and by disturbed cellular signaling.

Oxidative effects and non-cancer health effects of RFR

A new medical condition, so-called electrohypersensitivity (EHS), in which people suffer due to RFR exposure, has been described (Johansson, 2006). Typically, these persons suffer from skin- and mucosa-related symptoms (itching, smarting, pain, heat sensation), or heart and nervous system disorders after exposure to computer monitors, cell phones and other electromagnetic devices. This disorder is growing continuously: starting from 0.06% of the total population in 1985, this category now includes as much as 9–11% of the European population (Hallberg and Oberfeld, 2006). In Sweden, for example, EHS has become an officially recognized health impairment.

To that, a high percentage, up to 18–43% of young people, has recently been described to be suffering from headache/earache during or after cell phone conversations (Chu et al., 2011; Yakymenko et al., 2011). Likewise, a number of psychophysical and preclinical disorders including fatigue, irritation, headache, sleep disorders, hormonal imbalances were detected in high percent of people living nearby cell phone base transceiver stations (Buchner and Eger, 2011; Santini et al., 2002).

An allergy reaction to RFR in humans has been confirmed by a significant increase in the level of mast cells in skin of persons under exposure to electromagnetic devices (Johansson et al., 2001). Likewise, higher level of degranulated mast cells in dermis of EHS persons has been detected (Johansson, 2006). In turn, the activated mast cells can release histamine and other mediators of such reactions which include allergic hypersensitivity, itching, dermatoses, etc. Importantly, an implication of ROS in allergic reactions is rather clear nowadays. For example, in case of airway allergic inflammation, the lung cells generate superoxide in nanomolar concentrations following antigen challenges (Nagata, 2005). Then, mast cells generate ROS following aggregation of FcεRI, a high-affinity IgE receptor (Okayama, 2005). In addition, pollen NADPH oxidases rapidly increase the level of ROS in lung epithelium (Boldogh et al., 2005); and removal of pollen NADPH oxidases from the challenge material reduced antigen-induced allergic airway inflammation. Thus, it seems plausible that EHS-like conditions can be attributed at least partially to ROS overproduction in cells due to RFR exposures.

Oxidative effects and potential carcinogenicity of RFR

During recent years, a number of epidemiological studies indicated a significant increase in incidence of various types of tumors among long-term or "heavy" users of cellular phones (Yakymenko et al., 2011). Briefly, reports pointed to the increased risk in brain tumors (Cardis et al., 2010; Hardell and Carlberg, 2009; Hardell et al., 2007), acoustic neuroma (Hardell et al., 2005; Sato et al., 2011), tumors of parotid glands (Sadetzki et al., 2008), seminomas (Hardell et al., 2007), melanomas (Hardell et al., 2011) and lymphomas (Hardell et al., 2005) in these cohorts of people. To that, a significant increase in tumor incidence among people living nearby cellular base transceiver stations was also reported (Eger et al., 2004; Wolf and Wolf, 2007). Similarly, experimental evidences of cancer expansion in rodents caused by long-term low-intensity RFR exposure were published (Chou et al., 1992; Repacholi et al., 1997; Szmigielski et al., 1982; Toler et al., 1997). To that, activation of ODC was detected in RFR-exposed cells (Hoyto et al., 2007). ODC is involved in processes of cell growth and differentiation, and its activity is increased in tumor cells. Although overexpression of ODC is not sufficient for tumorigenic transformation, an increased activity of this enzyme was shown to promote the development of tumors from pre-tumor cells (Clifford et al., 1995).

Significant overproduction of ROS leads to oxidative stress in living cells, induces oxidative damage of DNA and can cause malignant transformation (Halliwell and Whiteman, 2004; Valko et al., 2007). It is known that in addition to mutagenic effects, ROS play a role as a second messenger for intracellular signaling cascades which can also induce oncogenic transformation (Valko et al., 2006). Earlier we hypothesized (Burlaka et al., 2013) that low-intensity RFR exposure leads to dysfunctions of mitochondria, which result in overproduction of superoxide and NO, and subsequently to ROS-mediated mutagenesis. To that, it is well established that oxidative stress is associated with carcinogenesis; for instance, the oxidative stress elicited by Membrane-Type 1 Matrix Metalloproteinase is implicated in both the pathogenesis and progression of prostate cancer (Nguyen et al., 2011). Similarly, a progressive elevation in mitochondrial ROS production (chronic ROS) under both hypoxia and/or low glucose,

which leads to stabilization of cells via increased HIF-2alpha expression, can eventually result in malignant transformation (Ralph et al., 2010). These data, together with the strong experimental evidences on activation of NADH oxidase under RFR exposure (Friedman et al., 2007) suggest that low-intensity RFR is a multifactorial stress factor for living cell, significant feature of which is oxidative effects and potential carcinogenicity as a result.

Conclusions

The analysis of modern data on biological effects of low-intensity RFR leads to a firm conclusion that this physical agent is a powerful oxidative stressor for living cell. The oxidative efficiency of RFR can be mediated via changes in activities of key ROS-generating systems, including mitochondria and non-phagocytic NADH oxidases, via direct effects on water molecules, and via induction of conformation changes in biologically important macromolecules. In turn, a broad biological potential of ROS and other free radicals, including both their mutagenic effects and their signaling regulatory potential, makes RFR a potentially hazardous factor for human health. We suggest minimizing the intensity and time of RFR exposures, and taking a precautionary approach towards wireless technologies in everyday human life.

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