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Effects of Cellular Phone- and Wi-Fi-Induced Electromagnetic Radiation on Oxidative Stress and Molecular Pathways in Brain

106

Mustafa Nazıroğlu and Hatice Akman

Contents

Abstract

It has been suggested that the widespread use of cellular telephones and wireless devices may result in increased health risks resulting from brain exposure to electromagnetic radiation (EMR). The situation has prompted many investigations into the interaction between EMR and neuronal cells, even at intensities not able to produce thermal effects. This chapter reviews the effects of Wi-Fi (2.45 GHz) EMR exposure on the central nervous system in humans and experimental animals.

Several studies have suggested that EMR emitted by wireless devices can interfere with learning and memory in both animal models and human, but the

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results obtained are controversial and the molecular basis of this interaction is still unclear. Electromagnetic radiation may induce some degenerative effects in the brain by increasing oxidative stress and DNA breakage plus interference with the blood–brain barrier permeability. There are also recent reports on the role of Wi-Fi and mobile phone frequencies on Ca^{2+} influx through Ca^{2+} channels. The EMR increases ROS production in the neurons through the activation of oxidant system including NADPH oxidase activity and nitric oxide production. These effects are accompanied by a decrease in brain tissue of enzymatic antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase together with a fall in the levels of nonenzymatic antioxidants such as glutathione and vitamin C.

Cell phone- and Wi-Fi-induced EMR appears to induce degenerative effects through increase of oxidative stress and decrease of antioxidants in the brain that affect neuronal physiological functions. Antioxidants seem to counteract the effects on the EMR, however.

Keywords

Antioxidants • Brain • Calcium ion • Oxidative stress • Wi-Fi

Abbreviations

DRG	Dorsal root ganglion
EEG	Electroencephalography
EMR	Electromagnetic radiation
GSH	Glutathione
GSH-Px	Glutathione peroxidase
PUFAs	Polyunsaturated fatty acids
ROS	Reactive oxygen species
SOD	Superoxide dismutase
TRP	Transient receptor potential
TRPM2	Melastatin-like transient receptor potential 2
VGCC	Voltage-gated calcium channels
WLAN	Wireless local area networks

Introduction

In recent times there has been a widespread increase in the use of wireless fidelity (Wi-Fi and 2.45 GHz) and cellular phone electromagnetic radiation (EMR)-emitting devices in industrial, scientific, medical, military, and domestic applications, with potential leakage of such radiation into the environment. The popularity of portable devices is increasing because it can be used at home, work, school, and hospitals. In terms of health risks, few data are available on the effect of exposure to these types of signal, and the main concern is focused on long-term exposure. For example, frequencies of the common household and work devices have, in some cases, been shown to be carcinogenic (Omura and Losco 1993; Kumar et al. 2011; Nazıroğlu et al. 2012a). Such studies suggest that biological systems may be

Table 106.1 Effects of Wi-Fi and cell phone frequencies on molecular pathways and cognitive functions in neuronal cells

Sample	Effects	Analyses	Frequency (MHz)	Reference
Rat DRG	Harmful	Ca^{2+} influx, cell viability, EEG, lipid peroxidation	2,450	Nazıroğlu et al. (2012b)
Rat cortical neurons	No effect	Potential amplitude and current–voltage relationship	900	Platano et al. (2007)
PC-12 neuroblastoma and hippocampal neurons	No effect	Multiple parameters (e.g., peak amplitude, integrated Ca^{2+} signal, recovery rates)	900	O'Connor et al. (2012)
Rat	No effect	Cognitive functions (maze test)	2,450	Cassel et al. (2004)
Rat	No effect	Cognitive functions (maze test)	2,450	Cobb et al. (2004)
Rat	No effect	Memory	900	Dubreuil et al. (2002, 2003)
Rat	No effects	Anxiety responses	2,450	Cosquer et al. (2005)
Rat	No effects	Apoptotic responses	2,450	Aït-Aïssa et al. (2010)
Human	Harmful	EEG, gender-related cortical excitability	2,400	Maganioti et al. (2010)
Rat	Decrease	Brain growth and development via protein kinase C (PKC) activity	2,450	Paulraj and Behari (2006b)

sensitive to some forms of EMR (Nazıroğlu et al. 2012a–e; Gümral et al. 2009). In fact, biological and health effects of radio frequency (RF)-induced EMR, in cell phone and wireless applications, on oxidative stress and molecular pathways in the brain are already well documented by an increasing number of in vivo (Nazıroğlu et al. 2012a), in vitro, and epidemiological studies (Behari 2010; Dasdag et al. 2009, 2012) (Table 106.1).

Very common, and constantly increasing, sources of RF exposure are wireless networks that allow high-speed internet access and services, such as Wi-Fi. Inevitably, there has been concern about possible health effects from such exposure; however, little research has been devoted to the investigation of the possible effects of Wi-Fi signal on biological systems.

Oxidative stress is defined as an imbalance between antioxidants and overproduction of reactive oxygen species (ROS), e.g., superoxide radical, hydrogen peroxide, and nitric oxide (NO) (Nazıroğlu et al. 2012a, b, 2013), that exceed cellular antioxidant defense mechanisms (Nazıroğlu 2011; Nazıroğlu et al. 2012c). Generation of ROS is ubiquitous since they are formed during physiological processes such as mitochondrial electron transport and phagocytosis (Espino et al. 2011; Espino et al. 2012). In order to scavenge ROS, various antioxidant

defense systems exist in the brain. Selenium is an essential dietary trace element which plays an important role in a number of biological processes (Nazıroğlu et al. 2012d). Glutathione peroxidase (GSH-Px), a selenium-containing enzyme, is responsible for the reduction of hydro- and organic peroxides in the presence of glutathione (GSH) (Nazıroglu 2009; Nazıroğlu et al. 2012e). Superoxide dismutase (SOD) contains zinc, copper, and manganese as cofactors, and it converts superoxide radical to hydrogen peroxide. The hydrogen peroxide is converted subsequently to water by catalase (it contains zinc and copper as cofactors) and GSH-Px (it contains selenium as cofactor) (Nazıroğlu 2012; Nazıroğlu et al. 2012e). GSH is a scavenger of hydroxyl radical and singlet oxygen and it participates in a wide range of cellular functions (Johnson et al. 2012). Vitamin E, alpha-tocopherol, is the most important antioxidant in the lipid phase of cells (Nazıroğlu 2007a). Vitamin C, as well as being a free radical scavenger, also transforms vitamin E to its active form (Bowman 2012).

If ROS are not controlled by the enzymatic and nonenzymatic antioxidants, they can cause oxidative injury, i.e., peroxidation of cell membrane phospholipids, lipids, proteins, and DNA. The brain is extremely susceptible to EMR-induced oxidative damage induced by these ROS because it generates very high levels of ROS because of its very high aerobic metabolism and blood flow and it has relatively poor enzymatic antioxidant defense (Nazıroğlu and Gümral 2009; Avci et al. 2012; Dasdag et al. 2012; Nazıroğlu et al. 2012c, d). The brain contains polyunsaturated fatty acids (PUFAs) which can be readily peroxidized (Ozmen et al. 2007). Brains are protected against Wi-Fi- and cell phone-induced oxidative damage by antioxidants such as Ginkgo biloba (Ilhan et al. 2004), melatonin (Sokolovic et al. 2008; Nazıroğlu et al. 2012d), L-carnitine, and selenium (Nazıroğlu and Gümral 2009).

In this review, we summarize likely the effects of cell phone and Wi-Fi frequencies on oxidative stress, molecular pathways, and physiological functions of human neurons as revealed by studies performed on experimental animals and cells in culture.

Safe Doses of Wi-Fi in Brain

Most of the studies that have been conducted while investigating the biological effects of Wi-Fi on humans have mainly dealt with the amount of energy absorbed by the human tissue. They are somewhat limited, however, with regard to measurements of the specific absorption rate (SAR). SAR is a rate of energy absorbed by a unit mass of the object and usually expressed by the parameter W/kg^2. We may liken the intensity of RF rate to a quantity of novalgin (analgesic) tablets. If, say, there are 100 mg of novalgin per tablet, we cannot decide anything about the efficacy of the tablets unless we also know the amount of the tablets taken, e.g., two tablets taken every 4 h (or 200 mg every 4 h). The amount of a drug absorbed into the body is the main determinant of its effect (Lai and Singh 1996).

There are also ongoing dosimetry studies that measure RF levels around the globe, including that coming from various sources including wireless local

area networks (WLANs) which indicate that the associated exposure level is low (Foster and Glaser 2007). Martínez-Búrdalo and Martin (2009) reported that measuring local energy SAR rates in different areas of the brain in a rat exposed to RF rate revealed that two brain regions that are spaced less than a millimeter apart can have more than a twofold difference in SAR. Martens et al. (1995) also reported that the peak (hot spot) for SAR in the head tissue of a user of a mobile telephone can range from 2–8 W/kg^2 per watt output of the device. The peak energy output of mobile telephones can range from 0.6–1 W, although the average output is closer to 0.6 than to 1.0 Studies have shown that neurological damage can be observed at exposure levels of 0.12 mW/kg (Eberhardt et al. 2008). This is less than one eighth of the average exposure level of 1 mW/kg found 150–200 m from a mobile phone mast. The researchers concluded that "the weakest fields are the biologically most harmful."

Yioultsis et al. (2002) studied the occurrence of considerable differences in electric field or SAR values. They also demonstrated high radiation absorption by the head, which, apart from any possible biological damage, caused a rise in brain temperature after a 10-min exposure. Although both SAR values and the thermal rise in the case of a WLAN are one or two orders of magnitude lower than before exposure, the issue of prolonged exposure is raised, since it is found that the safety limits for long exposure are also marginally violated.

Pinto et al. (2010) studied the dosimetry levels during exposure to the electromagnetic (EM) field associated with the Wi-Fi frequency band (2,412–2,484 MHz). The exposure system they developed allows experiments to be performed for the evaluation of biological effects of electromagnetic field exposure during early life. They found that average whole-body SAR drastically changes during the exposure period according to the size and weight of the new born mice.

Effects of Mobile Phone and Wi-Fi Frequencies on Oxidative Stress and Antioxidant Systems in Injury

The human body is equipped with a complete arsenal of defenses against environmental and internal hazards. Defenses against the so-called reactive oxygen species (ROS) such as superoxide anion, hydroxyl radical, and hydrogen peroxide are crucial in mitochondrial responses where they participate in physiological processes such as arachidonic acid cascade and redox cycle (Nazıroğlu 2011, 2012; Nazıroğlu et al. 2012b). The concentrations of ROS intermediates are actually kept under strict control by the activity of a complex antioxidant defense system. However, an uncontrolled production of ROS is liable to occur in several conditions leading to a situation known as "oxidative stress" where the highly ROS can attack many essential biomolecules (proteins, nucleic acids, and lipids) and even cell structures, causing oxidative damage. In fact, many pathological conditions are initiated or aggravated by such processes (Nazıroğlu 2007b; Behari 2010; Nazıroğlu et al. 2012c, 2013) (Table 106.2).

Table 106.2 Effects of Wi-Fi and cell phone frequencies on oxidative stress in the brain and neurons

Sample/animal	Effects	Analyses	Frequency (MHz)	Reference
Brain/mice	Harmful	Nitric oxide	2,450	Shahin et al. (2013)
DRG/rat	Harmful	Lipid peroxidation, GSH, GSH-Px	2,450	Nazıroğlu et al. (2012d)
Brain/rat	Harmful	Lipid peroxidation, nitric oxide	1,800	Avcı et al. (2012)
Brain/rat	Harmful	Beta amyloid protein, protein carbonyl, lipid peroxidation	900	Dasdag et al. (2012)
Fetal brain/rat	Harmful	Superoxide dismutase, glutathione peroxidase, malondialdehyde, noradrenaline, dopamine, and 5-hydroxyindoleacetic acid	900	Jing et al. (2012)
Cerebellum, hippocampus, frontal lobe/mice	Harmful	Several neural function-related proteins, heat shock proteins, cytoskeletal proteins, apoptosis, and oxidants	900/1,800	Fragopoulou et al. (2012)
Brain/rat	No effect	N-acetylaspartate, catalase, GSH-Px	3G	Dogan et al. (2012)
Brain/rat	Harmful	Total antioxidative capacity, catalase, total oxidant status, and oxidative stress index	900	Dasdag et al. (2009)
Brain/rat	No effect	Lipid peroxidation, GSH, GSH-Px, vitamin A, vitamin C, vitamin E	2,450	Nazıroğlu and Gumral (2009)
Brain/rat	Harmful	Lipid peroxidation, carbonyl group, catalase, xanthine oxidase	900	Sokolovic et al. (2008)
Brain/guinea pig	Harmful	Lipid peroxidation, glutathione, vitamin A, vitamin D, vitamin E, catalase	900	Meral et al. (2007)
Brain/rat	Harmful	Lipid peroxidation, nitric oxide, SOD, GSH-Px, xanthine oxidase, adenosine deaminase	900	İlhan et al. (2004)
Brain/rabbit	Harmful	Adenosine deaminase, xanthine oxidase, catalase, myeloperoxidase, SOD, GSH-Px, nitric oxide, lipid peroxidation	900	Irmak et al. (2002)

GSH glutathione, *GSH-Px* glutathione peroxidase, *SOD* superoxide dismutase

Microwave exposure results in dielectric heating. Dielectric heating comes about when an alternating electromagnetic field is applied to an imperfect dielectric material. EMR absorbers such as the brain and muscle contain a high percentage of water (as do most solid organs), while less heating occurs in tissues with low water content (e.g., fat). Radio frequency electrical conductivity refers to an alternating flow of electrons, while effective conductivity encompasses effects related to the

rotation of dipoles. Heating is more efficient in materials with a high conductivity at microwave frequencies, typically 915 MHz or 2.45 GHz for ablative technologies (Brace 2009). As explained, wireless can have different effects on health, and one of the possible actions could result from effects on the water content of our body because water molecules are strongly heated at microwave frequencies around 2.45 GHz Any tissue water can absorb much of this wireless radiation. When water, which is present in about 80 % of cells, is exposed to EMR, water split occurs through which a variety of ROS are formed in cells that contribute to cellular radiation injury (Gümral et al. 2009).

The EMR may disturb ROS metabolism by increasing their production or by decreasing antioxidant enzyme activity. Studies have also demonstrated that antioxidants such as melatonin, garlic acid, selenium, and L-carnitine prevent oxidative stress or apoptosis caused by EMR in animal brain (Köylü et al. 2006; Nazıroğlu and Gümral 2009; Avci et al. 2012). Chronic exposure to EMR decreases the activity of catalase, SOD, and GSH-Px and, thus, decreases the total antioxidant capacity. However, studies designed to measure lipid peroxidation levels and antioxidant enzyme activity have shown conflicting results (Dasdag et al. 2009; Köylü et al. 2006; Nazıroğlu and Gümral 2009; Kesari et al. 2010; Avci et al. 2012).

Use of mobile phones, and thus a potential source of electromagnetic radiation, has been increasing worldwide. Within the last decade, in vivo animal studies have shown that oxidative stress develops in response to cell phone radiation (Köylü et al. 2006; Meral et al. 2007). There are several reports that warn of possible mobile phone-induced oxidative stress in the brain (Fig. 106.1).

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone produced and released by the pineal gland in association with the suprachiasmatic nucleus and peripheral tissues and is considered a potent antioxidant that detoxifies a variety of ROS in many pathophysiological states (Ekmekcioglu 2006). Chemically, melatonin and its metabolites can function as endogenous free radical scavengers and broad-spectrum antioxidants (Bejarano et al. 2011; Espino et al. 2011). Köylü et al. (2006) reported that 900 MHz exposure-induced lipid peroxidation could be modulated in the brain cortex and hippocampus of rats by melatonin administration, and they concluded that melatonin may prevent EMR-induced oxidative changes in the hippocampus by strengthening the antioxidant defense system and thereby reducing oxidative stress products (Köylü et al. 2006). Similarly, Sokolovic et al. (2008) investigated protective effects of melatonin on antioxidant and oxidant values in long-term (40 and 60 days) 900 MHz-exposed rat brain. They observed increases in xanthine oxidase activity, carbonyl groups, and malondialdehyde (MDA) values by the exposures, although they reported a decrease in catalase activity in the brain after 40 and 60 days of exposure to the mobile phones. However, melatonin treatment modulated the increase in the MDA value and xanthine oxidase activity in the brain tissue after 40 days of exposure, while it was unable to prevent the decrease of catalase activity and increase of carbonyl group contents. They concluded that mobile phones caused oxidative damage biochemically by increasing the levels of MDA, carbonyl groups, and xanthine oxidase activity and decreasing catalase activity, although treatment with melatonin prevented oxidative damage in

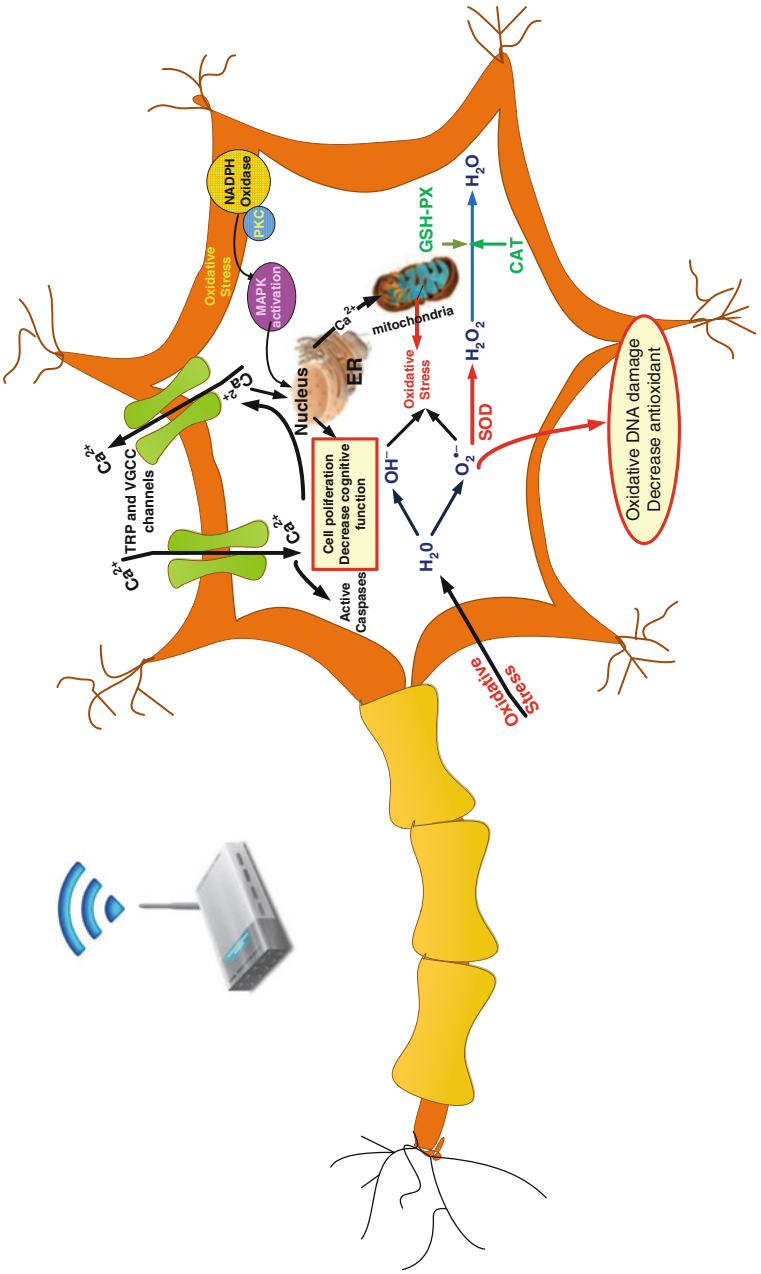

Fig. 106.1 (continued)

the brain. Kesari et al. (2012) investigated the effects of Wi-Fi (2.45 GHz)-induced EMR on melatonin, creatine kinase and caspase-3 activities, and Ca^{2+} concentration in the pineal gland and whole brain tissues of rats. They observed a decrease of melatonin but increases of both caspase-3 and creatine kinase activities, plus calcium ion concentration in the brain accompanying chronic exposure to EMR. Similarly, we have also recently observed that melatonin supplementation in dorsal root ganglion neurons and the brain of rats seems to have protective effects on the 2.45 GHz-induced increase Ca^{2+} influx, EEG records, and cell viability of the hormone through TRPM2 and voltage-gated Ca^{2+} channels (Nazıroğlu et al. 2012d, e).

Extracts of fresh garlic that are aged over a prolonged period to produce aged garlic extract contain antioxidant phytochemicals that prevent oxidant damage. These include selenium plus unique water flavonoids, notably allixin. Long-term storage of garlic extractions (up to 20 months) induces antioxidant properties by modifying unstable molecules possessing antioxidant activity, such as allicin, and increasing stable and highly bioavailable water-soluble organosulfur compounds, such as S-allyl cysteine and S-allylmercaptocysteine (Borek 2001). Avci et al. (2012) investigated the protective effects of garlic extracts on cell phone (1800 MHz)-induced oxidative stress changes in the brain of rats by monitoring brain advanced oxidation products including MDA and oxidized protein, serum NO, and paraoxonase values. They observed that exposure to EMR caused protein oxidation in the brain tissue and an increase in serum NO, but supplementation with garlic extracts reduced protein oxidation in the brain tissue although the extracts did not affect serum NO levels.

Recently, Dasdag et al. (2012) investigated long-term effects of 900 MHz EMR on beta amyloid protein, protein carbonyls, and malondialdehyde in the rat brain. They observed increases in all these parameters in the exposed rat brains. Jing et al. (2012) investigated effects of 900 MHz on SOD, GSH-Px, MDA, noradrenaline, dopamine, and 5-hydroxyindoleacetic acid values in fetal brain. They observed a decrease of antioxidant values and an increase of oxidative stress in the fetal brain, and they concluded that EMR induces oxidative toxic effects in fetal rat brain.

Fig. 106.1 Cells regulate intracellular Ca^{2+} levels lightly and over Ca^{2+} entry can lead to inappropriate activation of processes that normally operate at low levels, causing metabolic derangements and eventual cell death. For example, excessive elevations in intracellular Ca^{2+} through transient receptor potential (TRP) and voltage gated calcium channels (VGCC) may activate antioxidant degradation, induce formation of reactive oxygen species (ROS) or disrupt normal mitochondrial function leading to oxidative stress and bioenergetic failure. The rise in Ca^{2+} stimulates the release of superoxide radicals via activation of NADPH oxidase and MPAK activation. In the presence of superoxide dismutase (SOD), the superoxide radical is dismutased to hydrogen peroxide (H_2O_2). Then it was detoxified to water by catalase and glutathione peroxidase (GSH-Px) antioxidant enzymes. Antioxidants regulate EMR-induced Ca^{2+} influx into the cytosol by inhibition of ROS and regulation of TRP and VGCC. EMR such as mobile phones and wireless induces also apoptosis, caspase enzyme activitation and DNA damage through increase of ROS production

Fragopoulou et al. (2012) examined the effects of Wi-Fi- and cell phone-induced EMR on the proteome of cerebellum, hippocampus, and frontal lobe in Balb/c mice following long-term whole-body irradiation by the investigation of several neural function-related proteins (glial fibrillary acidic protein, alpha-synuclein, glia maturation factor beta, apolipoprotein E), heat shock proteins, and cytoskeletal proteins (neurofilaments and tropomodulin) and some enzymes of brain metabolism (aspartate aminotransferase, glutamate dehydrogenase). They observed changes in protein expression together with raised apoptosis and oxidative stress in the studied regions of the brain.

Dogan et al. (2012) investigated third-generation (3G) mobile phone-induced EMR on rat brain tissues by magnetic resonance spectroscopy and histopathological evaluations. Catalase (CAT) and glutathione peroxidase (GSH-Px) enzyme activities were also evaluated, but oxidation parameters such as MDA and NO were not measured in the study. They failed to observe statistically significant changes in the antioxidant and apoptosis values in the rat brain following the EMR exposure. Dasdag et al. (2009) investigated caspase-3 activity, p53 gene, total antioxidant capacity, catalase activity, total oxidant status, and oxidative stress index values in cell phone (900 MHz)-exposed rat brain, and they observed that apoptosis, total antioxidant capacity, and catalase in the rat brain were all negatively affected by the 900 MHz EMR.

Studies of vitamins C and E, the most prevalent natural antioxidant vitamins, suggest that the supplemental use of these vitamins may lower the risk for EMR events (Nazıroğlu et al. 2012b, 2013). Meral et al. (2007) investigated the effects of 900 MHz EMR on MDA, GSH, vitamin A, vitamin D, vitamin E, and catalase values in the brain of guinea pigs. They observed the increase of the MDA level and decrease in GSH level and CAT activity in brain tissues of EMF-exposed guinea pigs, although the A, E, and D vitamin concentrations did not change. Nazıroğlu and Gümral (2009) investigated protective effects of selenium and L-carnitine administrations on 2.45 GHz-induced EMR in the rat brain. They observed protective effects of the antioxidants on EEG records, GSH, vitamin E, and β-carotene values in the brain of rats.

A standardized extract of Ginkgo biloba (EGb 761) has been widely employed for its significant benefit in EMR-induced neurodegenerative disorders (Bridi et al. 2001). Ilhan et al. (2004) investigated the effect of Ginkgo biloba on cell phone (900 MHz)-induced oxidative damage in the brain tissue of rats. They observed the decrease of MDA and NO values and increase of SOD, GSH-Px, xanthine oxidase, and adenosine deaminase (ADA) values in the EMR-exposed rat brain. These alterations were prevented by Ginkgo biloba treatment. In addition, the protective effects of Ginkgo biloba were confirmed in the brain tissue by histological examination.

Irmak et al. (2002) investigated the influence of 900 MHz on oxidant and antioxidant levels in the serum and brain of rabbits by measurements of adenosine deaminase, xanthine oxidase, catalase, myeloperoxidase, SOD, and GSH-Px activities as well as NO and MDA levels. They observed that serum SOD activity increased although serum NO levels decreased in the EMR-exposed animals

compared to the sham group. Other parameters were not changed in the study. They did not observe changes in the values in the brain because the brain was protected from the EMR exposure by the skull bones of the head.

Shahin et al. (2013) investigated the Wi-Fi (2.45 GHz) EMR-induced stress response and its effect on implantation or pregnancy in the blood and brain of female mice. They observed the increase of oxidative stress values in the blood of the mice. In addition, DNA damage in the brain of the mice was increased by the exposure.

Yang et al. (2012) investigated the hippocampus, a sensitive target of EMR, to assess the changes in its stress-related gene and protein expression after EMF exposure. They targeted 2,048 candidate genes in the investigation, of which 23 were found to be upregulated and 18 downregulated. Within the upregulated category, two heat shock proteins were identified in the rat hippocampus. They concluded that exposure to the 2.45 GHz EMR elicits a stress response in the rat hippocampus.

Kesari et al. (2010) investigated the effects of 2.45 GHz on double-strand DNA breaks, antioxidant enzymes (catalase, SOD, and GSH-Px), and histone kinase activity in the whole brain of rats. They observed increases of comet head, tail length, and tail movement in exposed brain cells. They also observed decreases of histone kinase, GSH-Px, and SOD values and increase of catalase activities in the EMR-exposed brain. According to the results, they reported mutagenic and oxidant effects of the EMR on the brain in the rats.

Role of EMR in DNA Breaks and Blood–Brain Barrier

The EMR induces degenerative effects in the brain through increasing DNA breaks and by affecting the blood–brain barrier permeability.

DNA Breaks Studies

Lai and Singh (1996) found that even very low level microwave radiation leads to DNA breaks in the brain cells. EMR induces tissue degeneration through the overproduction of reactive oxygen species (ROS) and this causes breaks. Lai and Singh (2004) reported that the accumulation of DNA damage can cause cancer, and if a certain level of damage is exceeded, a cell will die. Cumulative DNA damage in nerve cells of the brain is associated with Alzheimer's, Huntington's, and Parkinson's diseases.

More recently, Paulraj and Behari (2006a, b) reported an increase in single-strand DNA breaks in the developing brain cells of rats that were exposed for 35 days to 2.45 and 16.5 GHz fields at 1 and 2.01 W/kg. In another study (Paulraj and Behari 2006b), it was reported that the increase of protein kinase C activity occurs in the brain of 2.45 GHz exposed rats. Nikolova et al. (2005) reported a low and transient increase in DNA double-strand breaks in mouse embryonic stem cells after acute exposure to a 1.7 GHz field.

Blood–Brain Barrier Permeability

It has been known for years that EMR has the potential to alter the permeability of the blood–brain barrier. Salford et al. (2003) and Nittby et al. (2009) report on various studies of the effect of EMR. The danger of a break in the blood–brain barrier is that the brain ceases to be protected from compounds in the blood that are harmful to the nervous system.

Salford et al. (1997) exposed rats to microwave radiation at an intensity equivalent to that received by a mobile phone user. They investigated the ease by which substances toxic to the central nervous system can cross over from the blood into the brain and found that the blood–brain barrier breaks down after a 2-min exposure. They demonstrated consequent neural damage especially in subjects of middle age and deduced that mobile phone use can precipitate degenerative brain effects. In addition, Nittby et al. (2008) and Nittby et al. (2009) and Salford (2007) have found that very low emission energy levels cause more leakage across the blood–brain barrier than higher levels.

Franke et al. (2005) reported that no changes in the blood–brain barrier permeability to sucrose occurred in response to constant exposure, over a period of 1–5 days, to a mobile phone signal at 1,800 MHz. Grafstrom et al. (2008) similarly could find no change in the permeability of the blood–brain barrier to several types of markers and observed no dark neurons or neuronal damage after exposing rats to a mobile phone 900 signal with an SAR of 0.6 or 60 mW/kg for 2 h per week, over a period of 55 weeks. Masuda et al. (2009) observed the passage of plasma protein albumin across the blood–brain barrier and no appearance of dark neurons in experiments. McQuade et al. (2009) observed no effect of a 30-min exposure to modulated GSM 915 MHz (two types of modulation: 217 Hz and 16 Hz) or to a continuous signal (SAR of 0.0018–20 W/kg in male rats). Poulletier De Gannes et al. (2009) also detected no effect on blood–brain barrier integrity or neuronal degeneration. These authors also assessed neuronal apoptosis. Cosquer et al. (2005) observed no effect of semi-chronic exposure to 2.45 GHz pulses (2 μs, 500 Hz) for 45 min per day over 10 days, using neither indirect observations based on cognitive tests nor by the passage of Evans blue dye across the blood–brain barrier (study carried out on 36 male rats). For the cognitive tests, the authors investigated whether radio frequency modified the behavioral response of the animals to the injection of a muscarinic antagonist (scopolamine) that crosses the blood–brain barrier only poorly. The response of the cage control rats differed from those seen in the sham-exposed and exposed rats (effect of stress), despite habituation to handling before testing.

Effects of Wi-Fi on Ca^{2+} Signaling in Brain and Neuron

The calcium ion (Ca^{2+}) is an important second messenger involved in a number of signal transduction pathways, which include muscle contraction, secretion, neuronal excitability, metabolism, cell proliferation, and cell death. Resting cytosolic free Ca^{2+} is generally maintained at very low levels (50–100 nM)

(Mattsson and Chan 2001) with Ca^{2+} influx to the cytoplasm being controlled by a variety of Ca^{2+} channels located on both the plasma and intracellular membranes. An assortment of Ca^{2+} channels exists on the plasma membrane. These include voltage-gated Ca^{2+} channels (VGCC), which are primarily found in excitable cells, transient receptor potential (TRP), store-operated channels, and receptor-operated channels found in both excitable and non-excitable cells (Nazıroğlu 2011; Nazıroğlu et al. 2012a, c). Store-operated channels, located on the plasma membrane, are activated when the endoplasmic/sarcoplasmic reticulum calcium stores are depleted. Activation of these channels allows an influx of Ca^{2+} and replenishment of the endoplasmic reticulum stores (Parekh and Putney 2005).

Platano et al. (2007) evaluated for the first time the possibility that acute exposure to GSM-modulated 900 MHz RF could modify the permeability of voltage-gated calcium channels in neurons. The experiments were performed in primary cultures of rat cortical neurons using the patch-clamp technique. They concluded that 900 MHz EMR did not alter potential amplitude or current–voltage relationship through voltage-gated calcium channels in neurons.

Nazıroğlu et al. (2012d) investigated the effects of 2.45 GHz exposure on the brain cortex and dorsal root ganglion (DRG) neuron oxidant and antioxidant redox systems and cytosolic Ca^{2+} release through TRP melastatin 2 (TRPM2) and VGCC, as well as the possible protective effects of melatonin on the brain and DRG injury induced by Wi-Fi EMR. They found that Wi-Fi (2.45 GHz) devices induce DRG oxidative toxicity through free cytosolic Ca^{2+} concentrations consequent to the activation of TRPM2 and VGCC. However, melatonin protects against 2.45 GHz and the Ca^{2+} abnormality by upregulating the brain EEG spikes of the animals.

O'Connar et al. (2010) investigated the effects of 900 MHz on Ca^{2+} signaling, and they used three cell types (human endothelial cells, PC-12 neuroblastoma, and primary hippocampal neurons) that have previously been suggested to be sensitive to radio frequency fields. They investigated multiple parameters including peak amplitude, integrated Ca^{2+} signal, and recovery rates to explore the potential impact of radio frequency field exposure on Ca^{2+} signals. They concluded that 900 MHz EMR had no effects on Ca^{2+} signaling in the cells.

Wi-Fi Exposure, Brain, and Cognitive Functions

Several lines of evidence suggest that protein kinase C (PKC) modulates ion conductance by phosphorylating membrane proteins such as channels, pumps, and ion exchange proteins, besides its role in the extrusion of Ca^{2+} immediately after its mobilization into the cytosol. The enzyme has also been implicated in the phosphorylation of several neuronal proteins, which are thought to regulate neurotransmitter release and long-term potentiation in memory formation (Tatsuo 1994). PKC has been involved in the regulation of a variety of cellular events including the modulation of receptor functions for major hormones and regulation of certain enzymes such as adenylate cyclase and ornithine decarboxylase. Protein kinase in

the membrane may be a target for low-level electromagnetic fields, which can lead sequentially to a variety of altered intracellular events in the cells (Byus et al. 1988).

Some reports indicated in humans and animals that cognitive functions were affected by EMR exposure. For example, Sienkiewicz et al. (2000) reported that EMR at 700 MHz can alter electrical activity in hippocampal slices of the brain in rats. Dubreuil et al. (2002, 2003) did not find any effect on spatial memory in rats subjected to head-only exposure to 900 MHz GSM signals. Likewise, a 10-day whole-body exposure to 900 MHz microwave radiation did not cause any deficit in the performance of mice in a spatial learning task. Cassel et al. (2004) and Cobb et al. (2004) reported that memory was not affected by whole-body exposure to 2.45 GHz EMR in rats tested in a maze. Kumin et al. (2007) found that 5-week exposure to a 900 MHz frequency signal (2 h per day, 5 days a week, SAR 3 W/kg) had no evident effect on the response of young rats in open field, the plus-maze, and acoustic startle tests. In conclusion it was shown that, in the water maze test, learning and memory were improved. In addition, Cosquer et al. (2005) indicated that anxiety responses were not changed in a maze test of rats by 2.45 GHz EMR exposure.

Paulraj and Behari (2006b) indicated that chronic exposures to 2.45 GHz may affect brain growth and development. This is because of the decrease in the PKC activity in the hippocampus. They also detected an increase in the glial cell population in the exposed group. Ammari et al. (2008) also reported that subchronic and chronic head-only exposure of rats to GSM 900 MHz signal (45 min, SAR 1.5 W/kg or 15 min, SAR 6 W/kg) did not induce spatial memory deficit in the radial arm maze in rats.

Maganioti et al. (2010) investigated whether the presence of Wi-Fi signal affects the pattern of EEG activity accompanying a short memory task (Wechsler test). They targeted electrophysiological brain activity, as reflected by alpha, beta, theta, and delta EEG bands, in association with cognitive task operations, and indicated that these investigations could be of value in identifying possible pathophysiological alterations evoked by Wi-Fi signals and their connection with gender. They found that Wi-Fi may influence normal physiology through changes in gender-related cortical excitability as it is reflected by the alpha and beta EEG frequencies.

Aït-Aïssa et al. (2010) assessed whether exposure to a Wi-Fi signal had an impact on the CNS of young rats exposed in utero and during early life. They found that whole-body in utero exposure with and without extended postnatal exposure to a Wi-Fi signal at SAR levels up to 4 W/kg for the dams and 12 W/kg for the pups did not trigger persistent astroglial activation or induce apoptosis in the brains of young rats. They concluded that prenatal exposure to Wi-Fi has no deleterious effects on the integrity of the developing rat brain.

Conclusions

We have reviewed the literature to better understand the effects of Wi-Fi on human health, especially on brain neural activity. Wi-Fi may affect cell function via nonthermal effects. The EMR exposure can increase ROS formation and decrease cognitive

function and antioxidant values by second messengers that cause increases in the activity of plasma membrane NADH oxidase and PKC activation. Prolonged exposure to EMR can also damage DNA which may accelerate neuronal cell death. Ca^{2+} is important in neuronal cells for physiological function and pathophysiological function such as cell proliferation and apoptosis. The results from relatively few recent papers indicate that Ca^{2+} influx is increased in neuronal cells through the activation of TRP channels and VGCC following EMR exposure. Future studies should therefore be aimed at identifying the specific intracellular pathways and calcium channels that transduce Wi-Fi-induced changes in calcium influx into signal capabilities of exposed brain and neurons.

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