Neurophysiological and Behavioral Dysfunctions After Electromagnetic Field Exposure: A Dose Response Relationship

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Abstract For decades, there has been an increasing concern about the potential hazards of ionizing and non-ionizing radiations on human health. This chapter provides several evidences related to pathophysiology of electromagnetic field (EMF) and its effects on different tissues and organs with special reference to neurophysiological and behavioral dysfunctions. Developing central nervous system (CNS) is extremely sensitive to EMF due to various factors especially due to presence of the high amount of water content, lipids and low amount of antioxidant enzymes. Therefore, the study is focused on the effects of radio frequency (RF) EMF and extremely low frequency magnetic field (ELF MF) on neurological disorders. The severity of effects always depends on exposure doses like, exposure duration, position of subjects, power density and field intensity, which could be measured in terms of specific absorption rate (SAR). There are several biomarkers, which are very useful to measure the radiation effects in both in vitro and in vivo model. The most intensely studied biomarkers by various researchers in CNS are protein kinase C, micronuclei, mitochondrial pathways, melatonin, calcium ion concentration, antioxidant enzymes like glutathione, superoxide dismutase, catalase etc. EMF may also lead to alterations in neurotransmission and consequently in cognitive and memory functions which are mainly linked to the brain hippocampus. Thus there are various histopathological aspects of hippocampus, which are studied and discussed in this chapter. Additionally, the dose response relationship between EMF and biological effects are discussed in this chapter.

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1 Introduction

Environment surrounding us, contains several type of contaminants, toxicants, pollutants and manmade exposures. These are biological, chemical or physical and could be classified under environmental toxicology. By applying the principles of biology, physics and chemistry, toxicologists can study the toxic behavior of man-made electromagnetic field (EMF) exposure. The hazards of radiofrequency electromagnetic radiation (RF-EMR) pervading the environment have now been increasingly realized and therefore, such radiations have been considered as an "electro-pollution" or "electrosmog" in the list of other environmental pollutants (air, water, soil, and noise pollution) (Behari 2009). Epidemiological evidences indicate that RF-EMF exposures are associated with adverse health effects such as tumor or cancer risk (Ahlbom et al. 2009). Not only the range of RF, but also extremely low frequency magnetic field (ELF MF) have been found to have causative effect on human health. Several epidemiological studies on RF-EMF or ELF MF exposure have investigated the health risks in populations living near cell phone towers, power lines, or who are in electrical occupations. The most common concerns include impaired sperm quality (Akdag et al. 1999; Cleary 1995; Kesari and Behari 2010), liver (Kumari et al. 2012), neurological dysfunctions (Sharma et al. 2014, 2016; Kesari et al. 2014; Kunjilwar and Behari 1993; Meena et al. 2014; Paulraj and Behari 2006) and histopathological changes such as cell injuries (Khayyat and Abou-zaid 2009; Kumari et al. 2012; Verschaeve 2009; Zare et al. 2007). Therefore, RF EMF and ELF MF were classified as a 'possibly carcinogenic to humans' (group 2B) by the International Agency for Research on Cancer (IARC 2002; Baan et al. 2011). Also at higher frequency level, International Commission on Non-Ionizing Radiation Protection reported that the specific absorption rate (*SAR*) *of* mobile phones is legally limited to 2.0 W/kg (ICNIRP 1998). In the USA, Canada and Australia, the maximum SAR level is limited to 1.6 and 2.0 W kg^{-1} in Europe (Dahal 2013), but most have an average SAR of $\sim$1.4 W/kg (Agarwal et al. 2011).

There are more than 2 billion mobile cellular phones or 4 billion people using mobile throughout the world (Stefanics et al. 2007; Roxanne 2009). These handholds mobile phones were normally started with 1G (first generation) and 2G (Second generation) and extended to 3G and 4G (third and fourth generation). With an increasing demand, now 5G (fifth generation) mobile phones are about to launch in market. With an increasing frequencies, the power density and exposure levels are also raised. Not only cell phone but also other electronic appliances like microwave oven has raised serious concern because of their frequent use in houses. The amount of RF EMF radiations absorbed by human tissue depends on the frequency, intensity, polarization and duration of exposure (Agarwal et al. 2011). It also depends on the level of doses, like for how long does a person is getting

exposure? In the case of chemical exposure, what is the amount or concentration level of intake? For the monitoring of radiation exposure, SAR is an important factor to measure the absorbed radiation into the body. The SAR value varies for each type of mobile phone and particular model based on usage conditions (Agarwal and Durairajanayagam 2015) and positions of keeping it with your body. Keeping cell phone near head while talking may lead to more absorption of power in the brain. This may cause an increase of up to 2 °C in the brain temperature on continuously talking for more than 20 min on phone. Microwave radiations have potential to penetrate the cranium, and nearly 40% of these can reach deeper into the brain (Barnett et al. 2007; Kang et al. 2001), where penetration depth is assumed to be 4–5 cm deep into the brain (Dimbylow and Mann 1994; Rothman et al. 1996). An interaction of microwave radiation with tissues arise as a result of mainly three processes; deep penetration into the tissue and their propagation into the living system, then the primary interaction of the waves within tissue, and the possible secondary effects arising from the primary interaction (Rachael 2010). The deep penetration of microwaves within the tissue or living cells is the process that causes the overproduction of free radicals/reactive oxygen species (ROS), will be discussed later in this chapter. Microwave induced oxidative stress may produce ROS which are reported to be the main cause of cellular damage or tissue injury (Dasdag et al. 2008; Kesari and Behari 2010, 2012). Therefore, this chapter provides several important findings related to pathophysiology of microwave radiation and its effects on different tissues and organs. These findings are in agreement with our own previous findings (Kesari et al. 2010a, b, 2012, 2013; Sharma et al. 2014), which indicate that the biological changes could occur due to a microwave exposure induced oxidative stress as also debated by several researchers (De-Iullis et al. 2009; Oktem et al. 2005).

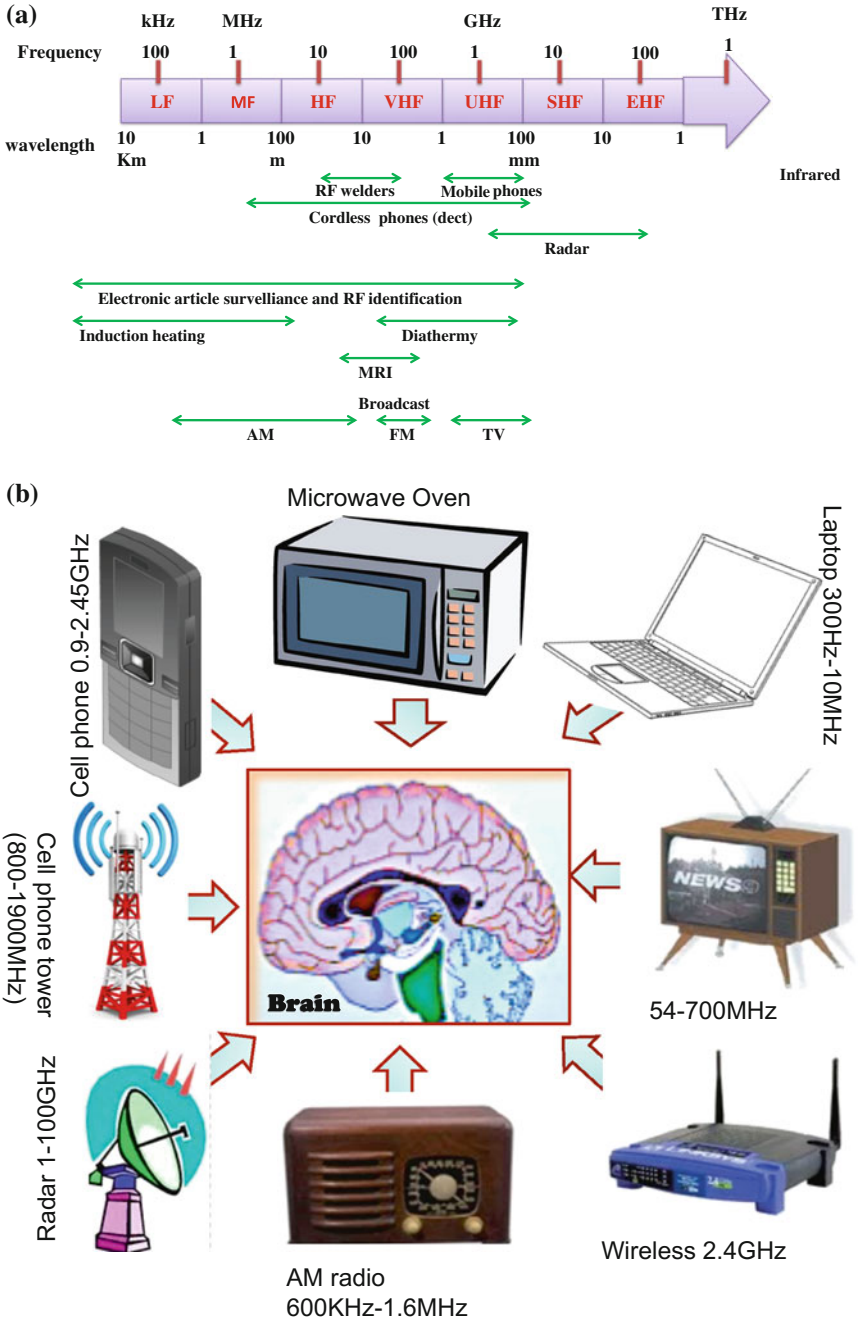
1.1 History and Sources of Electromagnetic Fields

The history of research on the biological effects of microwave radiation effectively begins with the development of radar early in World War II. Prior to this time, the energy levels at which microwaves had been produced were not sufficient to cause widespread concern about harmful effects. Before the invention of radar, artificially produced microwave energy was not a general environmental problem. However, as this field of research began to take shape, it did not do so in a vacuum. Well before the invention of radar, medical researchers had been interested in the controlled effect of RF energy on living things. Once it was discovered that radio waves could be used to heat body tissue, research was undertaken to study how such heating took place and its effect on the whole organism. As a consequence, both continuity and newness characterized this field of research during its early phase of development. Between the early 1940s and 1960, research on the biological effects of microwave radiation slowly shifted from its medical context and the search for

benefits to a military-industrial context and also search for hazards started. Polyashuck (1971) reported for the first time the effect of microwave radiation on the blood-brain barrier in 1971. Since the late 1970s, researches started which revealed that exposure to ELF electric and magnetic fields produces adverse health consequences. The sources of ELF MF comes from wherever electricity is generated or transmitted i.e. power lines, electric wiring etc. However, in many houses and office environments, individuals can experience perpetual exposure to "electromagnetic smog", with occasional peaks of relatively high EMF intensity. This has led to concerns that such radiation can affect health.

The classical example for natural source of non-ionizing radiation (NIR) is the sun and it is emitting ultraviolet radiation continuously. The most common source for NIR is transmission lines (50–60 Hz), computer monitor (60–90 Hz), AM radio transmissions (530–1600 kHz), thunderstorms (30–300 MHz), FM radio transmission (88–108 MHz), television transmissions (50–700 MHz), hand phones (850 MHz–2.4 GHz), wireless data and microwave ovens (2.45 GHz). In the last few decades, many places wireless technology has been introduced for telecommunication, but the long-term health effects of those waves are unpredictable and these emissions may affect human health. The term RF refers to the part of the electromagnetic spectrum that can be readily used for radio communication purposes which lie below the infrared region: specifically, frequencies in the range of 100 kHz to 300 GHz. Frequency bands within this range have been named more formally by the International Telecommunications Union (ITU). Figure 1a, shows these bands together with the ranges of frequencies commonly used for various applications, including those for telecommunications, in medicine, and in industry. Figure 1b, showing the several electromagnetic field exposure sources and effect on whole brain. Human exposure to RF field may arise from their deliberate use- for example, as a part of the global communication networks- or adventitiously, as a part of industrial and other processes utilizing RF energy. The term radio wave is used to denote a RFEMF that is transmitted from a source for communication purposes.

The microwave frequency spectrum ranges from 300 MHz to 300 GHz and RF radiation from 0.5 to 300 MHz. The sources of microwave and RF radiation are air traffic control systems, police and military radar, earth to satellite television broadcast systems, long distance telephone equipment, medical diathermy devices, cancer diagnostic and therapeutic (hyperthermia) equipment, microwave ovens, industrial applications and microwave generators. Among these, mobile phones have been available since the end of the 1980s and have become common in the general population in recent years. In most of the countries, today more than 80% of the population uses mobile phones (Feychting et al. 2005). This worldwide expansion of the use of mobile phones has made EMF exposure ubiquitous in modern society. Additional sources of exposure to RF fields are appearing from new technologies such as domestic meters and airport security scanners. As a consequence, intermediate frequency (IF) has been identified as newest source of exposure. It falls between the low frequency (Low frequency—0.1 Hz–1 kHz) and the RF (10 MHz–300 GHz). The major source of IF are some anti-theft devices


(a)
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Electronic article surveillance and RF identification
Induction heating
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MRI
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(b)
Microwave Oven
Laptop 300Hz-10MHz
Cell phone 0.9-2.45GHz
Cell phone tower (800-1900MHz)
Brain
54-700MHz
Radar 1-100GHz
AM radio
600KHz-1.6MHz
Wireless 2.4GHz

◂**Fig. 1** **a** The electromagnetic field spectrum. Abbreviations according to the International Telecommunications Union (ITU) band are given as LF: low frequency, MF: medium frequency, HF: high frequency, VHF: very high frequency, UHF: ultra-high frequency, SHF: super high frequency and EHF: extremely high frequency. **b** Effects of electromagnetic device usage on the CNS or whole brain. Usage of electromagnetic gadgets is associated with alterations in various neurological functions from the central nervous system. Figure shows the various sources of electromagnetic field exposure with their frequency range

operated at the exits of shops, induction hotplates, computers, compact fluorescent lamps, as well as some radio antennas.

1.2 EMF Exposure and Dosimetry

Recently, the National Toxicology Program (NTP) under the National Institutes of Health (NIH) in USA (Wyde et al. 2016) has released animal studies conducted on RF (cell phone) radiation exposure effect and cancer (glioma and malignant Schwannoma in heart). This is the largest ever-animal study reported tumor in the heart. Now the question is, how such a low frequency RF radiation may cause tumor? However, it is not easy to answer the question but possibility to explore by deciphering the role of dosimetry and field measurement within the body can be done. Cell phone emits RF-EMW to nearby relay base stations or antennas. Our bodies act as antennas that absorb the radiation and convert it into alternating eddy currents (DWB 2007). When speaking on the cell phone, the sound wave from speaker goes through a transmitter that converts the sound into a sine wave. The transmitter then sends the signal to the antenna, which then sends it out into space in all directions. The transmitter in cell phone operates on about 0.75–1 W of power, with 2 W at peak usage. This electric sine wave current running through the transmitter circuit also creates an EMF around it. As the electric current moves back and forth, the fields continue to build and collapse, forming EMR. Thus, cell phone radiation is generated in the transmitter, and is emitted through the antenna in the form of a radio wave (Agarwal et al. 2011; TECH 2007). The impact of these RF EMW on the human body is measured via a standardized unit called the SAR value.

The rate of absorption and the distribution of RFR energy in an organism depend on many factors. These include: the dielectric composition (i.e., ability to conduct electricity) of the irradiated tissue, e.g., bones, with a lower water content, absorb less of the energy than muscles; the size of the object relative to the wavelength of the RFR (thus, the frequency); shape, geometry, and orientation of the object; and configuration of the radiation, e.g., how close is the object from the RFR source? These factors make the distribution of energy absorbed in an irradiated organism extremely complex and non-uniform, and also lead to the formation of so called ‘hot spots’ of concentrated energy in the tissue (Lai 2002). For example, an experiment reported by Chou et al. (1985), measuring local energy absorption rates

(SARs) in different areas of the brain in a rat exposed to RFR, has shown that two brain regions less than a millimeter apart can have more than a two-fold difference in SAR.

At lower frequencies (<100 kHz), many biological effects are quantified in terms of current density in tissue and this parameter is most often used as a dosimetric quantity. At higher frequencies, many (but not all) interactions are due to the rate of energy deposition per unit mass. This is why the SAR is used as the dosimetric measure at these frequencies. It is expressed as $W\,kg^{-1}$. The SAR is thus the absorbed power by the absorbing mass. It is always challenging to measure SAR directly inside the human body. Therefore, the most obvious approach towards dosimetric analysis is to experimentally determine the SAR distribution in phantoms simulating animal and human bodies, as well as in real cadavers. Phantoms are well known as tissue equivalent material. It means that, the physical properties existing in human body can fulfill by using phantom material for SAR measurement. Using this makes easy to know the absorbance level in the brain or other delicate organs.

In general, the simple and standard procedure can be applied to calculate SAR values; E-field value is measured with a miniature E-field probe. Indeed, E-field probes/monopole antenna is the most appropriate sensor to measure the SAR, due to their sensitivity and fast response. E-field maybe calculated as-

$$\mathrm{SAR}(\mathrm{W/Kg}) = \sigma E^2 / \rho$$

where sigma (σ) is conductivity of the liquid and rho (ρ) is the density of liquid. The measured E-field values and SAR distribution are 1 and 10 g mass averaged SAR values.

2 Biomarkers of Neurological Dysfunction

Central nervous system (CNS) or brain is a very complicated part of our body and also a carrier for all other organs and metabolisms. Any damage or changes due to environmental exposure in brain may lead to serious health concerns. Biomarkers are often measured and evaluated to examine such changes in various part of human body, especially in brain. The brain is very sensitive and delicate part of human body on which any direct experiments are not possible. Though in vitro and in vivo methods are implemented to measure the neurological dysfunctions. Therefore, several biomarkers like, protein kinases, micronuclei, mitochondrial pathways, DNA damage etc. are very useful to measure the causative factors. An overview of EMF exposure effect on biomarkers, its mechanism and possible diseases are presented in Fig. 2.

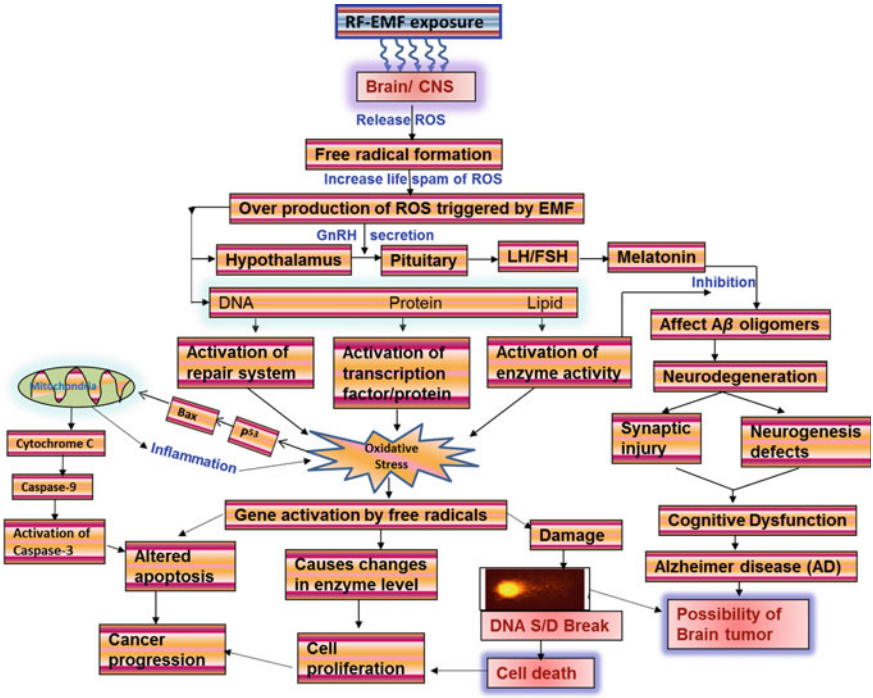

Fig. 2 Summary of the biological effects of RF-EMR exposure on central nervous system. This figure indicates enhanced ROS due to RF-EMR radiation can cause several changes at enzymatic and hormonal level, which may result Alzheimer disease and brain tumor. The activation of transcription and enzyme activity produce oxidative stress due to RF-EMF induced ROS formation. This results apoptosis by release of cytochrome c from mitochondria. The changes due to RF-EMF may enhance the DNA strand break by ROS formation and cause finally cell death

2.1 Protein Kinase C (PKC)

PKC is an isozyme and reported at least twelve in number. It differs in structure, biochemical properties, tissue distribution, subcellular localization, and substrate specificity. The first isoform that were Ca^{++}-activated, phospholipid-dependent protein kinases are ubiquitous enzymes that are highly enriched in the brain (Huang et al. 1986). Ca^{2+}-dependent PKC has been classified as conventional isozymes with α, β and γ. In late 1970s, it was first recognized as proteolytically activated serine/threonine kinase (Takai et al. 1977). PKC plays a major role in brain by regulating both pre and postsynaptic aspects of neurotransmission (Newton 1995; Nishizuka 1992; Stabel and Parker 1991). Any changes in the level of PKC and activation of various isozymes have resulted in brain tumor or neurodegeneration, like Alzheimer disease (Fig. 2). Therefore, researchers reported the structural basis for enhancement of long-term associated memory in single dendritic spines regulated by PKC (Hongpaisan and Alkon 2007). PKC play an important role in

neurological functions, which could be functional in mitochondria. Mitochondria are crucial regulators of energy metabolism and apoptotic pathways that have been closely linked to the pathogenesis of neurodegenerative disorders or malignancies. A malignancy like tumor promoter is well known receptor of PKC (Parker et al. 1984). Figure 2 shows the exposure pathway, that how the EMF interacts with skin and organs and producing free radicals in the cells. Free radicals generation enhance the ROS formation, which may effect several metabolic, enzymatic, transcriptional activity and lead to cell death.

Maximum quantity of PKC is found in the brain hippocampus, which is an integral part of the brain's limbic system. PKC also play an important role in behavior and learning memory—the cellular mechanism believed to underlie learning and memory. Damage to neurons in the hippocampus may therefore lead to impaired learning, memory and behavioral dysfunctions. PKC is known to exist as a family of closely related subspecies, has a heterogenous distribution in brain (with particularly high levels in presynaptic nerve terminals), and together with other kinases, appears to play a crucial role in the regulation of synaptic plasticity and various forms of learning and memory (discussed later in this chapter). Studies from our group have reported the PKC activity (in whole brain of Wistar rat) is reduced significantly ($P = 0.0483$) in EMF exposed group, as compared to sham exposed. Similarly, a significant decrease in the activity of PKC in developing rat brain was recorded more in hippocampus in comparison with whole brain data (Kesari et al. 2011b; Paulraj et al. 1999). PKC activity may play an important role in EMF-induced genotoxicity, and formation of micronuclei may lead to genomic instability.

2.2 Micronuclei: Genomic Instability

Micronuclei (MN) are small, nucleus-like structures present in the cell, especially relevant in the assessment of genotoxic effect. In cell culture studies, the elevated level of micronuclei in neuronal cell (SH-SY5Y) indicates that exposure to ELF MFs may induce genomic instability (GI) (Luukkonen et al. 2014), as also reported by Kesari et al. (2015). Micronuclei are a good biomarker for the detection of GI. Kesari et al. (2015) reported MF induced genomic instability in follow-up study of 15 and 30 days after 24 h of MF exposure. Any late effects due to environmental or chemical exposure may induce GI. Moreover, induced genomic instability (IGI) has also been investigated after exposure to a non-genotoxic agent (Korkalainen et al. 2012). Therefore, genomic instability or genotoxic effect is not only caused due to induced non-ionizing radiation but also non-genotoxic agents and ionizing radiation (well-known inducer of genomic instability) (Baverstock 2000). In the animal study, micronuclei in bone marrow or peripheral blood erythrocytes are widely accepted as a sensitive predictor of the clastogenic potential of chemical and radiation exposure (Criswell et al. 1998). Markers such as micronuclei, which are biomarkers of chromosome malsegregation and/or breakage, have been investigated

in patients affected by one of several neurodegenerative disorders and in groups of subjects at increased risk of neurodegeneration (Kesari et al. 2015, 2016: Trippi et al. 2001; Thomas et al. 2007; Jaworska et al. 2002; Scott et al. 1996; Vral et al. 1996; Migliore et al. 2011). Earlier, Kesari et al. (2011a) showed a significant decrease ($P < 0.002$) in micronuclei of mobile phone exposed group as compared with control group, where a decrease was recorded by comparing the ratio of PCE (polychromatic erythrocyte) and NCE (normochromatic erythrocyte) in animal blood cells. Kumar et al. (2010a, b) also showed the causative effect by lowered percentage of PCE/NCE at two frequency level of 10 and 50 GHz of exposure. The basic phenomenon of micronuclei shows that during RBC formation, erythroblasts expel their nucleus and may also damage the chromosome in the cytoplasm of young erythrocyte (in the form of micronuclei). Due to their relatively small size, the RF-induced MN is likely to change via a clastogenic effect. Therefore, during proliferation, the cells continue to divide and cause chromosomal damage such as breaks and exchanges, which eventually lead to formation of micronuclei. The significant changes in the frequency of micronucleated PCE in the experimental group is an indication of induced chromosomal damage. MN formation occurred with the loss of chromosome fragments due to microwave radiation. Such changes are responsible for the neurodegeneration or neurological diseases in developing brain, which may also cause Alzheimer's disease (Fig. 6).

2.3 The Mitochondrial Pathway: Role in Apoptosis

Mitochondria, which is well known powerhouse of the cell has the main site of oxygen metabolism, where cell consumed approximately 85–90% of the oxygen (Chance et al. 1979; Shigenaga et al. 1994). Oxygen takes part in glucose break down in mitochondria through oxidative phosphorylation and generates energy currency of cells i.e. ATP (Harvey et al. 1999). Mitochondria are vital cell organelles that capture the chemical energy of food to form ATP in the mitochondrial respiratory chain (MRC) (Schapira et al. 2006). Any mutation in mtDNA leads to impaired ATP generation and perturbed oxidative phosphorylation cascade that may further lock the neuronal function (Guido and John 2000). Therefore, a moderate increase in ROS levels can stimulate cell growth, proliferation or apoptosis and also cause cellular injury (e.g., damage to DNA, lipid membranes, and proteins) due to which it may lead to neuronal dementia. Mitochondrial dysfunctions and finally apoptosis have been reported as pathological cause for aging and neurodegenerative diseases in many dementias such as Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS) and amyolotrophic lateral sclerosis (ALS) (Uttara et al. 2009). Not only neuronal dysfunction, but also it is associated with a number of diseases for example including inherited mitochondrial disorders and lifestyle–related metabolic diseases, such as obesity. Obesity increases a risk of many diseases such as type 2 diabetes, cardiovascular diseases, cancers, inflammation, osteoarthritis, breathing disorders and depression, and significantly reduces the life

expectancy, up to 8–10 years in morbidly obese persons. Microwave radiation induced oxidative stress can modify the neuronal proteins and structural components in different neurological disorders leading to neuro-inflammation and loss of cognitive function in these dementias. Exposure to EMF may cause mutational changes in mitochondrial DNA in aged brain leading to oxidative stress and free radical mediated pathological changes in neurons. The cellular response to oxidative stress includes the release of mitochondrial cytochrome c and the induction of apoptosis as presented in Fig. 2.

The central role for mitochondria and cytochrome c in apoptosis was first acknowledged in a cell free system (Newmeyer et al. 1994; Liu et al. 1996). Cytochrome c released from the mitochondrial intermembrane space interacts with dATP and apoptotic protease activating factor (Apaf-1). After conformational changes enabling oligomerization of Apaf-1, the energy demanding aggregate called apoptosome is formed and recruits several procaspase-9 when in proximity becomes activated, leading to an expanding cascade of caspases, controlled digestion and degradation of the cell (Srinivasula et al. 1998; Li et al. 1997). Although the release of cytochrome c is a key event in apoptosis, the permeabilization process of the mitochondria is not fully understood. The findings of numerous Bcl-2 family members in the mitochondria raised the idea that these proteins were channel forming molecules (Muchmore et al. 1996). Although Bax oligomers can form transmembrane channels large enough for cytochrome c in experimental systems the existence of these channels in vivo remains to be conferred (Saito et al. 2000; Antonsson et al. 2000). As an alternative mechanism, Bcl-2 family proteins have been shown to regulate the opening and closing of a pre-existing channel in the outer mitochondrial membrane. This channel is called the permeability transition pore and includes the voltage dependent anion channel, the adenine nucleotide translocator and cyclophilin D (Zoratti et al. 2005). Figure 3 showing mitochondrial pathway of EMF exposure and the formation of apoptosis as discussed above.

2.4 Antioxidant Enzymes

Anti-oxidative enzymes can define the term oxidative stress. In general, antioxidants play an important role in distress of the cells or in other words, to protect the cells by oxidative damage. Oxidative damage can occur occasionally, anytime, anywhere and by any reason. Stress is the main factor for all internal causes to human body. Humans are constantly exposed to free radicals created by EMR from the manmade environment such as electro-pollution or electromagnetic-smog. Natural resources such as radon, cosmic radiation, as well as cellular metabolisms (respiratory burst, enzyme reactions) also add free radicals to the environment. The most common reported cellular free radicals are hydroxyl (OH·), superoxide ($O_2^{-}\cdot$) and nitric monoxide (NO·). Oxidative stress is a condition induced by oxygen and oxygen derived free radicals commonly known as reactive oxygen species

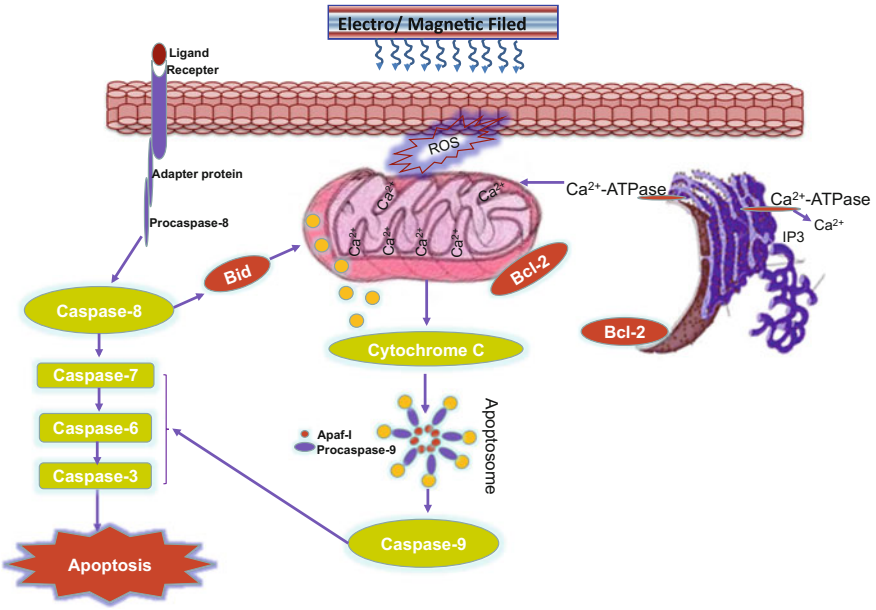

Fig. 3 One possible way in which electromagnetic fields induce changes in the apoptotic process in cells. The EMF, acting especially on Ca^{2+} ions, induces variations in ionic homeostasis. This perturbation of the Ca^{2+}, through its release from the endoplasmic reticulum and uptake by mitochondria initiates the apoptotic cascade. Through Bcl-2 action, this change in Ca^{2+} results in the release of cytochrome c from mitochondria, activation of caspase 9 along with other effector caspases and finally apoptosis or cell death

(ROS) (Schrader and Karnity 1994). ROS are particularly active in the brain and neuronal tissue as the excitatory amino acids and neurotransmitters, whose metabolism is factory of ROS, which are unique to the brain and serve as sources of oxidative stress (Uttara et al. 2009). ROS attack glial cells and neurons, which are post-mitotic cells and therefore, they are particularly sensitive to free radicals, leading to neuronal damage (Gilgun-Sherki et al. 2001).

Cellular antioxidants like superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) and malondialdehyde (MDA) are important markers of free radical generation. Adequate level of cellular antioxidants (SOD, CAT, GPx and lipid peroxide (LPO) maintain the free radicals scavenging potential in brain. A dose response relationship based on these enzymes at various power levels is also reported in this chapter later. Oxidative stress is the result of an imbalance between ROS generation and intrinsic ROS scavenging activities. Therefore, melatonin has been found to restrict the effect of EMF induced oxidative damage in the cells (Meena et al. 2014). Several studies from our group investigated significant changes in the level of SOD, GPx, CAT, lipid peroxidation (Chauhan et al. 2016; Sharma et al. 2014, 2016; Kesari et al. 2010a, b, 2011a, b, 2012; Kesari and Behari 2009).

2.5 Melatonin and Calcium Ion Concentration

Recently Meena et al. (2014) have reported the defensive property of melatonin against microwave radiations. All those diseases that involve the death of specific neurons due to changes in calcium ion concentration, melatonin level, protein kinases and oxidative damage may be classified as neurodegenerative diseases. As per neurological aspects studies shows that reduced melatonin can affect the brain and this might be leading to AD as also indicated in Fig. 2. Recently Kumar et al. (2011) also reported decreased level of melatonin after 2.45 GHz exposure of Wistar rats. Pineal melatonin is a vital natural neurohormone. It is a primary signaler of the daily cycle. Hence factors of microwave exposure that alter the melatonin/serotonin cycle can affect the brain and predictably all the vital organs. Melatonin is the most potent known natural antioxidant that scavenges free radicals to protect cells throughout the body, especially brain, heart and immune system.

Calcium ions play important roles in the function of the nervous system, such as the release of neurotransmitters and the actions of some neurotransmitter receptors. Thus, changes in calcium ion concentration could lead to alterations in neural functions. Ca^{2+} ions are essential in the regulation of the resting membrane potential and in the sequence of events in synaptic excitation (Ekert and Tillotson 1978; Seeman, 1972; Shanes 1958) and neurotransmitter release (Katz and Milledi 1967; Llinas and Nicholson 1975). The cell membrane is considered as the primary site for EMF interaction within the cellular systems. RF-EMW may alter intracellular calcium homeostasis by acting on plasma membrane calcium channels (Blackman et al. 1980). Rao et al. (2008) provided evidence supporting the theory that RF-EMW affects the plasma membrane. They studied the effects of RF-EMW on calcium dynamics in stem cell-derived neuronal cells and discovered a significant increase in intracellular calcium spikes in response to non-thermal RF-EMW. The pathway of release of calcium in mitochondria and possible mechanism is presented in Fig. 3.

3 Effects of RF-EMF on Developing CNS

Neurological effects may cause due to changes in the nervous system. The factors that act directly or indirectly in the nervous system causing morphological, chemical, or electrical changes, may lead to neurological disorders. The nervous system is an electrical organ. Thus, it should not be surprising that exposure to EMF could lead to neurological changes. Developing central nervous system (CNS) is especially sensitive to radiation exposure (UNSCEAR 2000; Di Toro et al. 2005). The immature antioxidants defenses and the higher abundance of free iron found in the developing CNS, together with the high proportion of dividing neuroblasts, might be some of the reasons for the high radiosensitivity and susceptibility of developing brain. Involvement of ROS in the pathophysiology of neurodegenerative diseases and brain

injury have been reported by several authors (Ciani et al. 1996; Marzatico et al. 2000; Liu et al. 2003).

Neurons are especially vulnerable to free radical attacks. Insufficient defense with exposure to excess ROS can lead to neuronal dysfunction and neuronal death (Bilici et al. 2001; Khanzode et al. 2003). Figure 2 shows the pathway of free radicals and neuronal dysfunctions by causing DNA damage, apoptosis and cell death. Clinical and laboratory animal studies have shown that environmental conditions during early life can alter brain and behavioral development (Heim et al. 1997; Daniels et al. 2004). Therefore, the issue of mobile phone use by children and adolescents for extended period was first raised and released by 'Stewart Report' constituted by the British independent expert group in 2000 (IEGMP 2000). Expert group reported the use of cell phone near head for longer time period leads to higher exposure in the brain. Theoretical studies on EMF absorption initially indicated a larger absorption in a child's head as compared with the head of an adult (Gandhi et al. 1996; Christ and Kuster 2005). The factors associated with brain and its development either in prenatal or postnatal condition are always important. However, the early foetal period is very active phase of cortical development in the rodent brain (Morgane et al. 1992). There are few reports on the effects of the low dose irradiation at the foetal period on the adult mouse behavior (Hossain and Uma Devi 2001).

3.1 Effects of EMF Exposure on Behavior and Cognition

For a decade, ELF is found to be more effective to cause behavioral changes in animal. ELF or electro-smog (networking of electric and magnetic field) can alter growth, morphology, differentiation, death program and nerve impulse transmission in the cells (Kerr et al. 1972; Pirozzoli et al. 2003; Grassi et al. 2004). Changes in behavior and cognition are important outcomes used to assess the effects of exposure of microwaves in the brain (D'Andrea et al. 2003; Keetley et al. 2006; Papageorgiou et al. 2006). ELF MF exposure causes the behavioral changes, which may lead to Alzheimer disease as discussed later in this article. Lai (1994) has reported the neurochemical and behavioral changes due to EMF exposure in CNS. Behavioral changes especially spatial learning of rodents owes relevance to human health (Anger 1991; Gallagher and Nicolle 1993). Spatial memory is a kind of short-term memory which is responsible for recording surroundings and spatial orientation. Spatial memory formation and consolidation depends on hippocampus, which reflects the influence of external stimulus on organism (Klur et al. 2009). Microwaves exposed rats showed retarded learning, indicating a deficit in spatial and cognitive function. A well-known test, Morris water maze, in which rat learn to locate a submerged platform in a circular pool of opaque water by using cues in the environment is a behavioral paradigm has been widely used to study spatial "reference" memory of rodents. Radial arm maze is used to study working performance of rodents. Radial Arm Maze (Olton and Samuelson 1976) and Morris Water Maze

test (Morris 1984; Morris et al. 1982), have been developed to assess rodent spatial memory and learning.

Liu et al. (2003) reported decline in learning and memory is associated with a significant increase in two parameters of oxidative stress in the brain i.e. levels of lipid peroxidation and protein oxidation. The exposure to EMF may have a facilitator effect on brain functioning, especially in tasks requiring attention and manipulation of information in working memory (Koivisto et al. 2000). Studies also indicate that microwave-induced hyperthermia can impair learning and memory (Moghimi et al. 2009). The hippocampus encodes the spatial relationships between components of scenes or contexts. However, in the absence of this, animals with hippocampal lesions will not be able to form the object-place configurations that are important in episodic memory (Lee and Solivan 2008; Narayanan et al. 2009). A review by Klann and Sweatt (2008) summarizes a contemporary model proposing a role for altered protein synthesis in memory formation and its subsequent stabilization. One defining aspect of the model is that altered protein synthesis serves as a trigger for memory consolidation. Thus, they proposed that specific alterations in the pattern of neuronal protein translation serve as an initial event in long-term memory formation. These specific alterations in protein readout result in the formation of a protein complex that then serves as a nidus for subsequent perpetuating reinforcement by a positive feedback mechanism (Fig. 4). Our earlier study on adult mice (6–8 weeks) exposed to 10 GHz microwaves reported that exposure to microwave radiation causes decrements in the ability of mice to learn the special memory task. This is correlated to the altered protein synthesis or less protein synthesis during this stage of translation, which stabilizes long-term memory (Sharma et al. 2014).

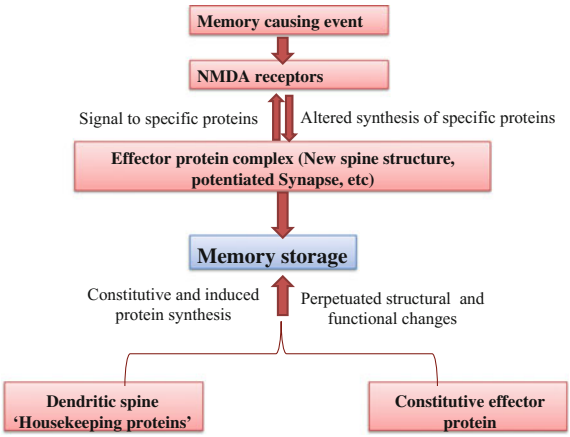

Fig. 4 Role for altered protein synthesis in memory formation and its subsequent stabilization (Klann and Sweatt 2008)

3.2 Effects of EMF on Neurotransmitters

Neurotransmitters are chemicals that carry (transmit) signals from one nerve cell to another. Neurotransmitters are released from one nerve cell and react with molecules called receptors on another nerve cell. The reaction alters the activity of the second nerve cell. Activities in nerve cell could also change the properties of these receptors (mainly by changing the concentration or the affinity of the receptors to neurotransmitters). Manikonda et al. (2007) reported effects of chronic ELF EMF exposure on N-methyl-D-aspartate receptors (NMDA) in the hippocampus of the rat brain. Salunke et al. (2013) reported that ELF EMF-induced anxiety in the rat involved NDMA receptor in the brain. There is a report on the effects of magnetic field serotonin and dopamine receptors in the rat brain (Janac et al. 2009). Changes in a subtype of serotonin receptors 5HT(2A) in the prefrontal cortex were reported. However, Masuda et al. (2011) reported that another types of serotonin receptor 5HT (1B) were not significantly affected after magnetic field exposure in an in vitro experiment. However, the 5HT(2A) receptors, particularly in frontal cortex, are related to psychiatric syndromes of depression in humans. Kitaoka et al. (2013) and Szemerszky et al. (2010) have reported depression-like behavior in the mice and rats, respectively, after chronic exposure to magnetic field. There are two reports on dopamine receptors. Sin et al. (2011) reported an increase in D-1 dopamine receptor and activity in the striatum of the rat after magnetic field exposure. Dopamine in striatum is involved in Parkinson's disease. Wang et al. (2008) reported that ELF MF potentiated morphine-induced decrease in D-2 dopamine receptor. The implication of these data is not readily clear. Both D-1 and D-2 dopamine receptors in the brain are involved in depression and drug addiction. However, study on the cholinergic system by Ravera et al. (2010) reported changes in the enzyme acetylcholinesterase in cell membrane isolated from the cerebellum after magnetic field exposure. Interestingly, these researchers also reported 'frequency window' effects in their experiment. Window effects could be observed at a certain range(s) of EMF frequency or intensity. Study by Fournier et al. (2012) reported 'intensity window' effect of ELF magnetic field on neurodevelopment in rat. The cholinergic systems in the brain play a major role in learning and memory functions.

3.3 Histopathological Alterations in Brain Induced by EMF

The possible effect of RF exposure on nervous system has prompted investigations with animal model mostly focusing on biochemical and morphological alterations. Neuronal damages in cortex, hippocampus, cerebellum, and basal ganglia due to RF exposure have also been reported earlier (Mausset et al. 2001; Salford et al. 2003). Results from our research group also suggested that the reduction in number of pyramidal cells and cerebral cortex of neuronal cells after microwaves exposure might be due to the radiosensitive nature of the cells. Salford et al. (2003) reported

highly significant ($p < 0.002$) evidence for neuronal damage in the cortex, hippocampus, and basal ganglia in the brain of exposed rats to GSM mobile phone of different strengths. The noxious effects of radiation on the cerebellar cortex have been reported by Sisodia and Singh (2009). The hippocampus and olfactory bulb are two structures of CNS continuing neurogenesis after birth. Thus perfect operation of these structures should be affected by neurogenesis (Bruel-Jungerman et al. 2007). Bas et al. (2009) demonstrated that postnatal exposure to 900 MHz EMF reduced the number of pyramidal cells in the cornu ammonis (CA) of the female rat hippocampus. Consequently, Sonmez et al. (2010) determined that a long term EMF exposure may lead to reduced purkinje cells number in female rat cerebellum. Bagher et al. (2008) exposed BALB/c mice to 50 Hz, 0.5 mT EMF for 4 h per day, 6 days per week for 2 months. They concluded that long term exposure to EMF has detrimental effects on the morphological changes of neurons of the frontal cortex and may lead to degenerative phenomenon on pyramidal cells.

Most of the studies done in hippocampus are focused on CA1 region. Figure 5 shows pyramidal neuronal cells in CA1 region of mice hippocampus. Region CA1 receives input from the CA3 subfield, EC layer III and the nucleus reuniens of thalamus (which project only to the terminal apical dendritic tufts in the stratum lacunosum-moleculare). In turn, CA1 projects the subiculum as well as sending information along the aforementioned output paths of the hippocampus. Dorsal CA1 and dorsal CA3 sub regions of the hippocampus have been shown to play an important role in mediating temporal order memory for spatial location information. Histopathological changes in CA1 region were observed in our studies after microwaves exposures in mice brain are in a line with results of Miranda et al. (2006), where they showed that a functional hippocampus is required for the acquisition of spatial tasks in the Morris water maze. Current models of memory consolidation

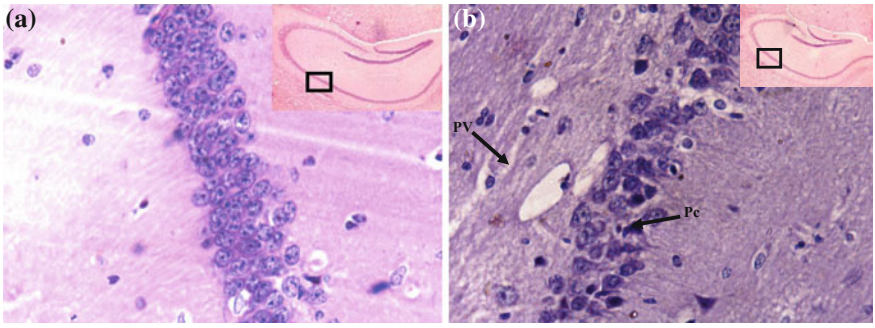

Fig. 5 The effects of 10 GHz microwaves exposure for 30 days (2 h/day) in the diencephalon region of hippocampus. **a** Sham exposed group: the hippocampal neurons and vessels exhibited a regular arrangement, with distinct edges, clear nucleus and nucleolus, and no significant necrosis of pyramidal neurons. **b** Microwaves exposed group: reduced density of pyramidal cells with edema, and neurons exhibited pyknosis (P) and anachromasis with widened perivasicular space (PV). (HE staining, original magnification × 400)

(Dudai 2004; Nader 2003) assume that the storage of long-term memory (LTM) is associated with gene expression, new protein synthesis, and synaptic remodeling. The CA1 region also appears to be involved in retrieval after longer time delays, with rats lessoned in the CA1 region having no difficulty in encoding new information but impaired in retrieval after 24-h of interval (Jerman et al. 2006; Vago and Kesner 2005). Evidences reviewed elsewhere (Rolls and Kesner 2006) indicates that the CA1 region makes a special contribution to the temporal aspects of memory, including associations over a delay period, sequence memory and order memory. The CA1 network is thought to play an important role in retrieval of information to the neocortex, consequently affecting others parts of the brain involved in guiding behavior. Maskey et al. (2010) investigated the effect of RF exposure on rat hippocampus by using both CB (Calbindin) and glial fibrillary acidic protein (GFAP) specific antibodies. The immune-histochemical result shows decrease in CB immuno-reactivity (IR) with the loss of interneurons and pyramidal cells in CA1 region as well as granule cells. Also, an increase in GFAP IR was observed in the hippocampus of E1.6. The change of reactive astrocytosis, which commonly, precedes neuronal death (Petito and Halaby 1993) also supported by Ammari et al. (2008).

4 EMF Links to Alzheimer Disease

Alzheimer's disease (AD) is a most common progressive neurodegenerative disorder of the brain, where Przedborski (2003) reported about the process for the loss of structure and function of neurons. However, if these neuronal changes cannot be compensated may lead to neurodegenerative disease. There are several factors, which are responsible for such disease. One of the important factors is ELF-MF, which is a part of occupational as well as environmental exposure. Several in vivo, in vitro and epidemiological studies have been carried out on manmade as well as natural exposure conditions. The risk in population living near power lines, in electrical occupations and in other groups exposed to ELF-MF have been investigated. The epidemiological studies have provided evidence that exposure to ELF magnetic fields is associated with increased risk of AD (e.g., Håkansson et al. 2003; Feychting et al. 2003; Hug et al. 2006; Huss et al. 2009; García et al. 2008; Röösli et al. 2007). Interestingly these epidemiological associations have been reported at very low magnetic field levels (of the order of 1 μT), much lower than the exposure guidelines (100–500 μT). Therefore, it is important to determine whether the epidemiological findings reflect a true causal relationship with ELF. Most of the epidemiological research on occupational exposure focused on frequency ranging between 3 and 3000 Hz and primarily to ELF-MF (50–60 Hz). Based on these frequencies and certain intensities, there are several studies suggesting that ELF MFs affect the nervous system in humans and animals (e.g., Lyskov et al. 1993a, b, 2001; Fu et al. 2008; Liu et al. 2008; Falone et al. 2008), but considering this the evidence is partly inconsistent and the relevance of the findings to AD is not so well known.

When we talk about biological effect due to MF exposure at the frequency 50/60 Hz, it does not transfer energy to cells in sufficient amounts to directly damage DNA. A possible mechanism of interaction between MF exposure and biological damage is a process where involvement of free radical may have derived from oxygen metabolism is known as ROS. Therefore, a moderate increase in ROS levels can stimulate cell growth and proliferation and also cause cellular injury (e.g., damage to DNA, lipid membranes, and proteins) due to which it may lead to produce neuronal dementia. However, there are several other end points (such as, increased oxidative stress, accumulation of Aβ, mitochondrial dysfunction, DNA damage) which are impetus for apoptosis in AD (Canu and Calissano 2003; Mattson and Magnus 2006). Other potential pathways, which may involve in relationship between ELF-MF and AD include apoptosis and necrosis in brain cells. The pathway for EMF exposure and AD is presented in Fig. 6. Researchers also proposed possible hypothesis that ELF-MF affects the cell membrane structure and permeability to small molecules (Baureus et al. 2003; Grassi et al. 2004; Marino et al. 2003).

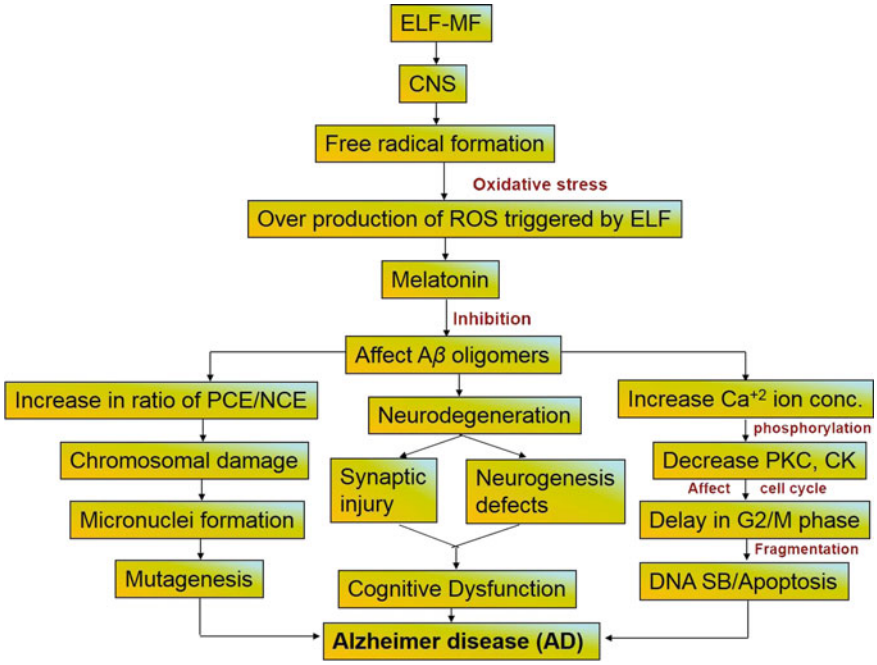

Fig. 6 Interaction mechanism between free radical formation and cell function due to radiofrequency/microwave radiation exposure on CNS. The pathway shows that enhanced ROS due to ELF-MF exposure can cause several changes at enzymatic and hormonal level, which may result Alzheimer disease. ELF induced ROS formation can increase the genotoxic level by increasing micronucleus formation, affect Aβ oligomers and cause neurodegeneration due to which cognitive dysfunctions occur and cause AD. Also another hypothesis shows increased calcium ion concentration and decreased protein kinases (i.e. PKC, histone kinases), delay G2/M phase (DNA synthesis phase) and damage DNA due to which it may transform into AD

Therefore, ELF-MF probably interfere with chemical reactions (O_2, H_2O_2, OH) involves free radical production (Simko and Mattsson 2004). Further, Falone et al. (2007) reported changes in redox and or differentiation status in neuroblastoma cells after short term MF exposure. Indeed, since last few years due to ELF exposure, several data show the redox-related cellular changes (Regoli et al. 2005; Wolf et al. 2005; Zwirska-Korczala et al. 2005). Also study from Katsir and Parola (1998) reported an increase in cell proliferation. Authors concluded that this was due to higher exposure over the frequency (50–100 Hz) and intensity (0.1–0.7 mT) range, where 70% increase in proliferation was recorded with exposure to 100 Hz at 0.7 mT. Though the study presented here suggest the effects due to ELF-MF also depend on exposure parameters like field densities, intensities, modulation and dose response relationship between EMF and biological parameters.

5 Exposure Response Relationship

It is always worthy to discuss about the dose response relationship between EMF exposure and biological effects. The levels of dose for every purpose are very important factor. Recently, Kesari et al. (2016) conducted cell culture studies on two different neuronal cell lines and field intensities (10, 30 and 100 μT). Authors showed strong dose effect at higher field intensity but also suggest that the threshold, if it exists, for biological responses to 50 Hz MFs is of lower intensity at 10 μT or less. From our previous findings at several field intensities (900 MHz, 2.45 and 50 GHz) it is aimed to investigate the dose response relationship between RF-EMF exposure and brain dysfunctions. Overall, the data of this study (Fig. 7a–c) is adopted from our previous findings of Kesari and Behari (2009) and Kesari et al. (2010a, 2011b). Dose response effects on antioxidant enzymes were mostly consistent with a conventional exposure-response relationship: when significant effects were observed, the point estimates of the effect size increased with increasing microwave field strength (900 MHz, 2.45 and 50 GHz).

5.1 Experimental Data Evaluation

For easier judgment of the exposure-response relationships, the data on SOD (Fig. 7a), GPx (Fig. 7b) and CAT (Fig. 7c) were plotted as a function of microwave frequencies. Relative value in RF-EMF-treated group was calculated by dividing the value observed in RF-EMF group by the value observed in control group. SOD, GPx and CAT showed a rising trend of effect size with increasing microwave frequencies in whole brain (Fig. 7a–c). In SOD and GPx, the RF-EMF effect was more in 50 GHz of microwave-exposed group by compared with 900 MHz and 2.45 GHz of exposure group. As described above, this effect was significant at all three frequencies in the

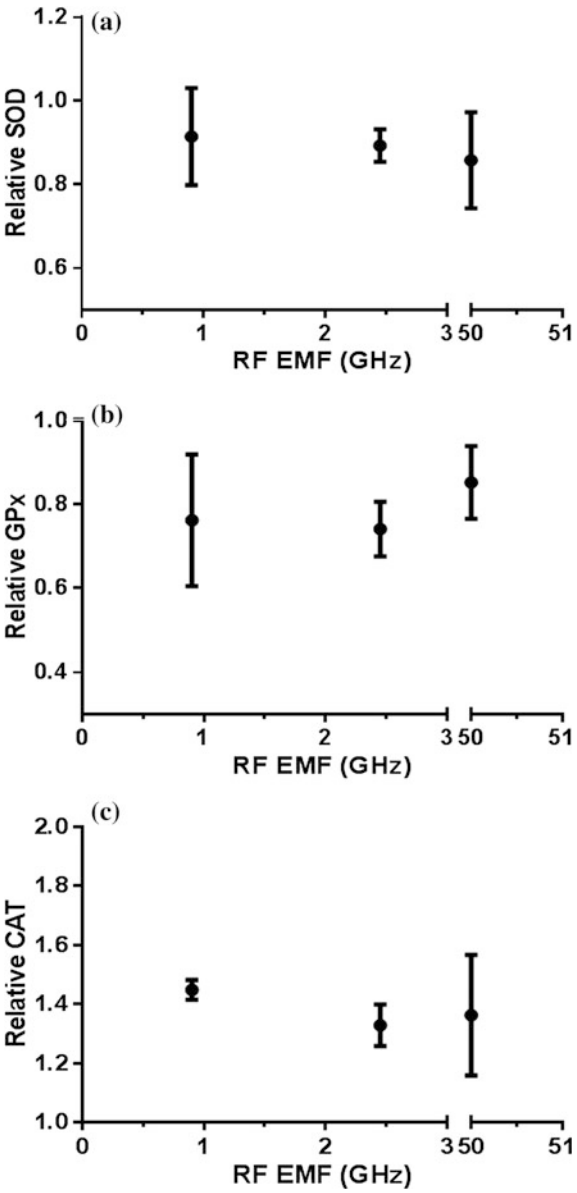

Fig. 7 Exposure-response relationship for antioxidant enzymes, superoxide dismutase (**a**), glutathione peroxide (**b**) and catalase (**c**) in whole brain of male Wistar rat, exposed to 900 MHz (or 0.9 GHz), 2.45 GHz and 50 GHz RF-EMF. The data are given as relative values (value observed in RF-EMF exposed sample divided by the value measured in corresponding non-exposed sample), with 95% confidence intervals

previous studies, where significant ($p < 0.05$) decrease in the level of brain GPx, SOD and increase in the level of catalase activity were investigated in exposed group by comparing with control ones (Kesari and Behari 2009; Kesari et al. 2010a, 2011b). Including these studies, several associated dose response relationship is also discussed in this manuscript to explore the mechanism of field interaction.

Lai and Singh (1995) first reported on dose-dependent changes at DNA level induced by low intensity microwave RFR. A dose-dependent increase in DNA single and double strand breaks in brain cells (exposed at 0.6 and 1.2 W/Kg whole body specific absorption rate) were found after two hours of exposure to 2450 MHz RFR. Several other studies also suggested that microwave induced oxidative stress is able to cause DNA damage in sperm cells (Meena et al. 2014; Kumar et al. 2014) and increased the level of micronuclei at various power densities (Kesari et al. 2011b; Kumar et al. 2010a, b). The results of Ivancsits et al. (2002, 2003a, b) indicate that the interaction of these fields with DNA is quite complicated and apparently depends on many factors, such as the mode of exposure, the type of cells, and the intensity and duration of exposure. Recently, Jankovic et al. (2014) also investigated that the nature and extent of the effect depend on the frequency of microwaves and the total energy absorbed by the microorganisms was dose dependent. Authors reported that low energy, low frequency microwaves enhance the growth of microorganisms, whereas high energy, high frequency microwaves destroy the microorganisms. Therefore, it is obvious to say here that the biological effect of RF-EMF mainly depends on the exposure level, duration of exposure, and the position or organ of body that was exposed to RF Radiation.

6 Conclusion

In light of present debate, we have concluded that neurophysiological and behavioral dysfunctions are affected by EMF exposure. The effects could be measured in terms of one or more of the several biomarkers like protein kinase C, micronuclei, mitochondrial pathways, melatonin, calcium ion concentration, antioxidant enzymes like glutathione, superoxide dismutase, and catalase. Therefore, we hypothesize that any tumor promoting effects of RF-EMF might be due to the effect it has on these biomarkers which may accelerate neuronal cell death and promote neurodegenerative processes (AD) or brain carcinogenesis (Fig. 2). This study also concludes that the dose response relationship is an important factor in an association between RF-EMF and neuronal dysfunction. This leads to a possible conclusion that the effects of RF EMF are cumulative and dose dependent in terms of exposure time and field strength.

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