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REVIEW PAPER

Interaction of Radiofrequency Radiation with Biological Systems: A Comprehensive Update on Recent Challenges

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ABSTRACT

Rapid advancement of radiofrequency (RF)-driven technologies has greatly affected our everyday lives. Increasing evidence led by in-vitro, in-vivo studies, epidemiological and clinical trials indicates that RF interacts considerably well with biological systems in various ways depending on different exposure parameters and properties of biological materials. Besides their innumerable benefits in different sectors of commercial and military fields, they can induce alterations in many physiological functions of the body, which may culminate into adverse human health consequences. The present article explicitly addresses the RF-based technologies and their applications, fundamentals of RF energy interaction with biological systems, exposure parameters, and dosimetry studies along with thermal and non-thermal effects on different vital organs at molecular and cellular levels. Further, this article outlines the limitations of RF-induced biological effect studies, status of risk assessment, safety levels and its future perspectives.

Keywords: Biological systems; Radiation exposure; Radiofrequency; Safety levels; Thermal and non-thermal effects.

1. INTRODUCTION

The electromagnetic (EM) spectrum is distribution of EM waves in order of their frequency and wavelength extending from gamma rays to extremely-low radiofrequency (RF). This bandwidth distribution of energy consists majorly of two separate groups: non-ionising and ionising radiations. Ionising radiations includes gamma rays, X-rays, ultraviolet light, visible light spectrum and infra-red rays. The microwaves and radiowaves are grouped under non-ionising radiations. The ionising radiations interact with cellular and sub-cellular structures at atomic and subatomic level, break chemical bonds of biomolecules, hydrogen bonds of DNA bases and generate free radicals, which can lead to mutations that may culminate into development of tumor and even cell death. On the other hand, non-ionising radiations, which possess low-energy density considered safe by scientific world.

The RF radiations are subset of EM spectrum comprising frequencies ranges from 3 kHz to 300 GHz range. RF has been categorised under different bandwidths on basis of their frequency range as specified by the International Telecommunication Union (ITU) standards (Table 1). From last few decades, RF-based technological advancements are touching every aspect of our day to day life. Commercial and military systems employed widespread uses of RF-electromagnetic radiation (RF-EMR) emitting telecommunication devices (mobile phones, wireless networks), military radar, satellite communication etc. However, after mid-nineties it has been noticed that ever-increasing applications of non-ionising RF-based technologies are accompanied by adverse health effects like oxidative damage, physiological disorders, DNA damages and apoptosis[1-4]. Recently, the findings of different scientific studies reported that RF-EMR exposure exert various alterations in physiological functions of the body such as thermoregulatory responses, inflammation, modulations in cardiovascular, endocrine, neurological systems and vulnerability in dermal, ophthalmological and reproductive system[5-9].

There are basically two type of RF-EMR interaction mechanisms: thermal and non-thermal. In recent trends, beside the RF-induced hyperthermic effects, concerns are growing majorly over elusive non-thermal effects, which alter tissue, cellular and molecular physiology by temperature-independent cascades[10-11]. However, mechanisms of action of RF-EMF interaction with biological entities at different physiological stages are still not clearly understood.

Therefore, more scientific dosimetry studies are needed to validate and for better understanding of molecular insights at cellular and tissue levels. Present article comprehensively addressed the findings of recent studies and relevant literature on RF-based technologies and their applications, relevance of exposure parameters, in-vitro and in-vivo studies, epidemiological and clinical investigations to understand the fundamentals of biological interaction mechanisms of RF-EMF and associated potential health risks. Consequently, such studies could provide valuable information for development of safety levels and maximum permissible exposure (MPE) limits that need to be taken care for wellness of human health.

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Table 1. Designated electromagnetic field bands with specifically allocated bandwidth of frequency and wavelength with their potential civilian and military applications[4]

Radiofrequency Bands	Frequency	Wavelength	Applications
High frequency	3-30 MHz	100-10 m	Aviation air-to-ground communications, Global Maritime Safety System
Very high frequency	30 – 300 MHz	10-1 m	FM radio broadcasting, television broadcasting, two way land mobile radio systems
L band	1-2 GHz	30-15 cm	GPS, mobile phones (GSM), amateur radio, microwave ovens
S band	2-4 GHz	15-7.5 cm	Microwave (MW), mobile phones, wireless LAN, bluetooth
C band	4-8 GHz	7.5-3.75 cm	Long-distance radio telecommunications
X band	8-12 GHz	3.75-2.5 cm	Satellite communications, radar, terrestrial, broadband
K_u band	12-18 GHz	2.5-1.67 cm	Satellite communications
K band	18-27 GHz	1.67-1.11 cm	Radar, satellite communications, astronomical observations
K_a band	26.5-40 GHz	1.11-7.5 mm	Satellite communications
V band	40-75 GHz	7.5-4 mm	Millimeter wave (MMW) radar research
W band	75-90 GHz	4-2.73 mm	Satellite communications, radar research, military radar targeting and some non-military applications
F band	90 -110 GHz	3.3 - 2.1 mm	Modern radars, communications satellites, satellite television broadcast
D band	110-170 GHz	2.7- 1.8	High frequency microwave radio relay, remote sensing, energy weapon, MMW scanner

2. RF RADIATION-BIOLOGICAL SYSTEM INTERACTION

RF-EMF wave has four fate when it strikes a biological body: absorption, transmission, reflection and scattering. These interactions induce an electric and magnetic field in the biological systems, which eventually may cause alteration in normal physiological balance. Magnitude of interaction of RF-EMF radiations depends on its frequencies, waveforms, strength of the induced fields, pulsed wave (PW)/ continuous wave (CW) field, exposure duration, and the rate at which energy deposited or absorbed in the biological systems also known as 'specific absorption rate' (SAR). These physical variables manifested into exposed biological tissue based on its dielectric constant, conductivity, penetration depth into the biological tissues, ionisation potential, induced charges, dipole relaxation etc. which culminated into alteration of biological molecules implicated at cellular and molecular levels. Therefore, to understand specific interaction mechanisms underlying biological effects is important to establish the relationships among various observed effects in different biological models at different exposure dosage[12-13].

Another phenomenon studied extensively to unravel the molecular mechanism, generally elucidates the ionisation potential of RF-radiations. Exposure of RF fields with high magnitude, intensity and longer duration could lead to the absorption and accumulation of energy RF photons, potentially enough to produce significant alterations in the chemical nature of biomolecules to interact with other cellular components and may affect their normal physiological functioning. The intense RF radiations are also known to induce dipoles in the water molecules and other polar biochemical molecules in tissues. These induced dipoles accumulate in the interacting molecules after a certain relaxation time-period and generate altered polarity in other biological molecules. These RF-induced alterations may have serious implications over health that needs to be addressed with valid scientific evidences[14].

3. HEALTH IMPLICATIONS OF RF RADIATION

Biological interactions of RF-EMF radiation exposure are principally governed by two major effect i.e. thermal and non-thermal.

3.1 Thermal Effects

Interactions with RF-EMF leads to heating of biological tissues, such effects imparted are known as 'thermal effects. Human body is unable to cope up heat after a threshold limit under certain conditions. The rate and magnitude of temperature rise due to RF-EMF exposure depends on various factors such as wave forms (frequency, phase difference, intensity) which governs the penetration power of RF into the biological tissue. Another major factor involved is SAR of tissue, which depends on thickness, duration of exposure, shape and size, orientation, coefficient of permissitivity of tissue, efficiency of heat dissipation, leads to deposition of energy into biological tissue. Blood circulation is primarily responsible for dissipating body heat to cope up the excessive heat generated during RF-EMF exposure. Therefore, eyes are known to be highly vulnerable to heating by high energy RF-

EMF, owing to relative lack of available blood flow to dissipate the excessive heat load. Likewise, reproductive, nervous, cardiovascular and endocrine systems also respond promptly to RF-induced thermal changes[8]. Such effects persist mainly due to the localised elevation in tissue temperature through the induction of electric charges on cell membrane, tissue surface and biologically active molecule[12]. These alterations upset thermoregulatory mechanisms which eventually engender severe thermal consequences into exposed biological tissue over prolonged exposures[13-14].

Furthermore, RF-EMF radiation-induced agitation (vibrational, rotational, linear) in polar molecules is also supposed to account for temperature enhancement as one of its plausible effect[14,15]. It has been reported that RF exposures for longer duration may lead to degradation of biomolecules, which confers the alteration in vitamins and oxidative balance of sensitive organs like brain[16]. These major cascades foster new chain of molecular events in complex machinery of cell to respond and to cope up with such effects, by enhancing the cell resistance, over-expressing heat shock proteins (HSP), heat shock cognates (HSC), cell cycle arrest, checking DNA integrity etc., which can confer the body to survive through these stress conditions[17].

3.2 NON-THERMAL EFFECTS

Majority of the studies done till date is on thermal effects of RF-EMR, however, there are non-thermal effects as another interaction mechanism not caused by either direct increase in temperature, but due to cellular and molecular alterations or transformations. The non-thermal biological effects of RF-EMR have been attributed to the interaction with biological membrane and alter its function, which may possibly cause depolarisation of cell membrane[12]. These non-thermal interactions accounts for RF-induced signal transduction pathways.

Oxidative stress and generation of reactive oxygen species (ROS) have been reported to be one of major consequences of non-thermal effect of RF-EMF[18]. Rifat[19], *et al.* demonstrated that exposure to 10 GHz microwave radiation caused significant alterations in the lipid peroxidation and glutathione levels (GSH) and protein content of different organs in mice and these effects were modulated by supplementation of *Prunus domestica* fruit extract to some extent. Some of the documented RF-induced biological effects include changes in induction of HSPs[20], decreased endogenous antioxidants[21], reduced ornithine decarboxylase (ODC) and protein kinase C (PKC) activities[22], alteration of intracellular calcium concentration[23], effects on spatial memory[24-25], changes in blood-brain barrier (BBB) permeability[26], genotoxicity and DNA strand breakage[27,28]. It has been shown that short-term (2-24 h/d up to a week) exposure of extremely low frequency-EMF may increase innate immune response, whereas long-term (2-24 h/d up to 8 yrs) exposure may lead to decrease in adaptive immune response[29]. To surmise, both RF-induced thermal and non-thermal effects confer their biological consequences through different mechanisms. However, it is still matter of an open debate to ascertain the non-thermal biological effects of RF-EMR.

4. EFFECT OF RF EXPOSURE ON BIOLOGICAL SYSTEMS

Numerous studies have been reported to understand the potential risk of RF-EMR on various vital organ systems. A diagrammatic representation of potential risks of radiofrequency radiation exposure on biological systems has shown in Fig. 1.

4.1 Effects of RF on Nervous System

The nervous system, brain, spinal cord, blood-brain-barrier are considered as sensitive targets for RF radiation exposure. Since neuronal cells lost their regenerative capabilities once damaged, therefore nervous system could be more susceptible to RF-EMF radiations. Several epidemiological reports suggested direct links of RF field exposure with several neurodegenerative disorders like Alzheimer, Parkinson, motor neuron disease and multiple sclerosis among the people continually getting exposed. Several in-vivo studies suggested that expression of stress related genes, proteins and transcription factors altered subjected to RF-EMF at different frequencies and power densities. In one such study, rats were exposed at power density 0.21 mW/cm^2, SAR 0.014 W/kg for 2 h/day continuously for 45 days and demonstrated reduction in melatonin, increased caspase-3, creatine kinase, and calcium ion, which might be responsible for brain injury[30]. RF exposure of 112 MHz modulated to 16 Hz at power density 1 mW/cm^2, SAR 75 mW/kg for chronic exposure of 35 days showed enhance ODC activity and Ca^{2+} ion efflux in rat brain indicating potential health hazard[31]. Furthermore, Sokolovic[32], *et al.*, reported that rats exposed to 900 MHz (SAR 0.043–0.135 W/kg) caused oxidative damage, as evidenced by an increased lipid peroxidation level, xanthine oxidase and decreased catalase activity. Furthermore, they exhibited that therapeutic intervention with melatonin significantly reduced RF-induced oxidative stress in rat brain.

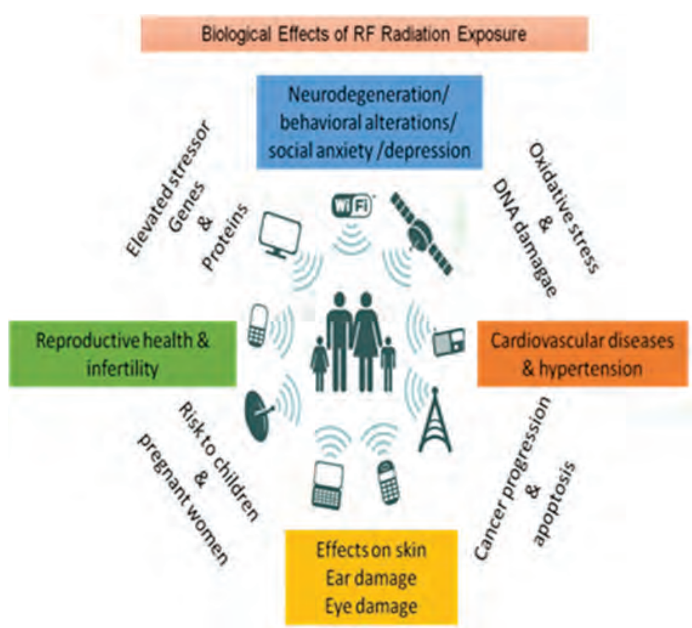

Figure 1. Diagrammatic representation of potential risks of radiofrequency radiation exposure on biological systems.

In-vitro studies conducted showed effect on intracellular Ca^{2+} levels in neuroblastoma cell line and its release was found to be decreased at synaptic junctions, which could reduce transmission of neuronal signals[33]. Exposure at SAR 1.2 W/Kg at constant power density 2 mW/cm^2 caused a deficit in spatial 'reference' memory in the rat, delay in spontaneous reaction time, and impairment of long term memory[34]. Narayanan[35], *et al.* revealed that exposure of GSM (900 MHz and 1.8 GHz) by giving 50 missed calls within 1 h/day continuously for 4 weeks damaged the hippocampus and amygdala region affecting learning behavior, memory retention period, emotions, anxiety and depression. Another study investigated the effect of RF radiation on male rat brain exposed for 2 h/day for 35 days at power density 0.34 mW/cm^2, SAR 0.11 W/kg showed decrease histone kinase, GSH, superoxide dismutase (SOD) and increase catalase activity, which leads to neuronal impairment[36].

4.2 Effect of RF on Reproductive System

The reproductive organs are susceptible to high temperatures; therefore, it is very much prone to affected by exposure of RF radiations. Several reports have suggested deterioration in production of sperm cells, motility and overall reproductive health. Erogul[37], *et al.* studied the effects of GSM 900 MHz, 2 W peak power, average power density 0.02 mW/cm^2 on semen samples from 27 healthy male volunteers and reported adverse effects on sperm motility with behavioral and structural changes. Yan[38], *et al.* exposed rats to 1.9 GHz (800 MHz digital and analog) two times daily for 3 h continuously for 18 week and exhibited a significantly higher number of incidences of sperm cell death. Aitken[39], *et al.* reported changes in genome wide expression pattern after exposing mice to 900 MHz, 12 h/day for 7 day at SAR 90 mW/Kg with evident genotoxic effect in epididymal spermatozoa. A significant decrease in PKC, total sperm count was reported in male rats exposed to mobile phone frequency with duration of 2 h/day for 35 day at SAR 0.9 W/kg[40]. These studies ascertain the possible role of ROS behind these detrimental effects of RF-EMF. Agarwal[41], *et al.* conducted an in-vitro study to evaluate the effects of cellular phone 870 MHz in talk mode for 1 h, and suggested significant decrease in sperm motility, viability, increase in ROS level, but no significant change in DNA damage. Dasdag[42], *et al.* showed that mobile phone exposure of 2 h/day, 7 day/week for 10 month did not induce apoptosis evident by no change in levels of active (cleaved) caspase-3 levels in testis of exposed rats. Recent findings from same group shed light into the effects of RF exposure to 2.45 GHz emitted from Wi-Fi systems (2.42 mW/kg) on male rats for 24 h/day for 12 month and demonstrated significant increase in the head defects of sperms, decreased weight of epididymis, seminal vesicles, diameter of seminiferous tubule and tunica albuginea thickness[43].

4.3 Effect of RF on Endocrine System

Alteration in the hormonal balance due to non-specific stressors (heat) and other specific stressors (non-ionising radiations) can have devastating effects on human health. Mechanistic studies have shown that effect of RF-EMF exposure on endocrine system is similar in response as in thermal stress. Shahryar[44], *et al.* studied the effect of cellular phone (900 MHz) in Syrian hamster, after exposure of 1 h/day for 10 and 50 day, and it was reported that long-term exposure led to increase levels of serum cortisol, T4, but decreased T3 levels suggesting damage to the endocrine system. Eskander[45], *et al.* assessed the effect of RF emitted from mobile phones, base stations on human's hormone profiles in blood samples collected regularly at first, third and sixth year and revealed significant reduction in plasma ACTH, serum cortisol, thyroid hormone T_3 and prolactin levels in young females, and testosterone levels in males[45]. The study showed vulnerability of pituitary-adrenal axis to long-term RF exposure. In another study, rats were exposed to 1.8 GHz, power density 208 uW/cm^2, SAR 0.5762 W/kg for 2 h/day for 32 day and suggested disturbances in circadian rhythm of synthesis of plasma melatonin and testosterone levels after RF exposure[46]. In a recent study, the effect of chronic EMF exposure from radar at 8-12 GHz and 12.5-18 GHz were evaluated. The study reported a significant decreased melatonin and increased serotonin levels in occupational group exposed with service period of more than 10 year[6].

4.4 Effect of RF on Skin and Eye

Skin is the outermost layer of the body and acts as primary defence barrier against RF-EMF exposure. Moreover, high proliferation rate of new skin cells make them more vulnerable to RF-radiation exposure. The RF radiations at high dosage and for longer duration may lead to generation of oxidative stress, DNA adducts and cancer. A study led by Ennamany[47], *et al.* investigated the molecular events after 6 h exposure of 900 MHz on human epidermis and studied transcriptomic variation of 600 gene in keratinocytes and clearly indicated that exposure to RF induced dramatic modulation of transcriptome in the stress/ inflammatory response genes.

Millenbaugh[48], *et al.* studied microarray analysis after exposing rats to 35 GHz at power density 75 mW/cm^2 for 6 and 24 h to explore the RF radiation-induced cellular and molecular responses and compared it with external environmental heat exposure at 42 ^{O}C. They demonstrated alteration in gene expression profile of rat skin exposed to 35 GHz as evident by significant modulation in the expression of 56 gene at 6h and 58 gene at 24 h involved in transcriptional regulation, redox homeostasis, inflammation, structural protein integrity and extracellular matrix turnover. Real-time RT-PCR revealed that more genes related to extracellular matrix structure and chemokine activity were found to be altered at 24 h by 35 GHz, 75 mW/cm^2 and suggested that prolonged RF radiation exposure induced thermal related stress, injury in skin and initiating repair processes involving inflammation and tissue matrix recovery.

Similar to skin, the lens of the eyes are also highly sensitive to RF radiation attributed to fact that eye lenses have limited ability to dissipate heat as they are devoid of blood vessels. Yao[49], *et al.* demonstrated that 2 h of intermittent acute exposure to 1.8 GHz GSM signal with SAR of 1, 2, 3, and 4 W/kg in human lens epithelial cells led to DNA damage mainly single stand break and may be associated with the increased ROS production, however, they have further explained that superimposition of RF with EM-noise could inhibit RF-induced ROs production and DNA damage. Majorly eyes of infant and elderly people are very much sensitive to RF-radiation exposure. Hence, there is high need of valuable input in the repository data to understand the effects of RF-induced radiations on eye more precisely.

4.5 Effects of RF on Cardiovascular System

Scientific studies have reported that effect of RF-EMF exposure on cardiovascular systems is attributed to its characteristic to increase the body temperature which leads to anomalies like increase in heart rate, blood pressure, blood flow, damage to epidermal layer along with myocardial muscles[50]. Epidemiological studies conducted by Vangelova[51]*, et al.* assessed the long-term effects of RF radiation on radio relay station operators and found significant increase in systolic and diastolic blood pressure along with increase in low-density lipoprotein. This study renders that RF exposure contributes to adverse effect on cardiovascular systems associated with hypertensive and dydlipidemia.

Kumar & Behari[52] exposed rats to 10 GHz for 45 days, 2 h/day at SAR 0.014 W/Kg with constant power density of 0.21 mW/cm^2 and 50 GHz for 45 day, 2 h/day at SAR 8 x 10^{-4} W/Kg with constant power density of 0.86 µW/cm^2 and reported DNA damage apparent by formations of micronuclei, ROS production with evident change in glutathione peroxidase, SOD, catalase activities in blood cells, serum and indicated genotoxic effects of RF exposure. In a retrospective cohort study of prolonged exposure to military radar operators exposed at 3 GHz, 5.5 GHz, and 9.4 GHz exhibited oxidative stress evident by decreased glutathione and increased MDA levels and cytogenetic alterations in peripheral blood lymphocytes which may impose to increase in incidence of hemolymphatic cancer[53]. Garaj[54]*, et al.* exhibited that radar workers exposed to 1.25-1.35 GHz at power density 10-20 mW/cm^2 expressed significant number of chromatid breaks in peripheral blood leukocytes.

5. LIMITATIONS OF STUDIES OF RF-BASED BIOLOGICAL EFFECT

Limited database with lack of proper knowledge for mechanisms of interaction of RF-EMF radiations due to consternations on RF exposure dosimetry parameters are major obstacles for development of safety measures guidelines for RF radiations. International RF exposure standard regulating bodies such as International Commission on Non-Ionising Radiation Protection (ICNIRP), Institute of Electrical and Electronics Engineers (IEEE), International Telecommunication Union (ITU) and National Council on Radiation Protection (NCRP) laid the guidelines for safety levels with respect to human exposure to RF-EMF. Recommendations made by IEEE in C95.7 (TM)-2014 standard, designed to prevent humans being exposed to RF field from 3 kHz to 300 GHz, based on interpretation of relevant studies, literature available and SAR values (Table 2)[3]. However, parameters like, frequency, duration, dosage, intensity, power density, orientation of body, age of subject, gender etc. should be consider while contemplating SAR values. Another problem in doing epidemiological surveys is, volunteers also avoid revealing their experiences, working in controlled and uncontrolled environment for such studies. Such circumstances create a loophole in creating a pool of database and reliable literature in this research area. Systematic experimental planning of dosimetry studies need to be chosen judicially and unprejudiced for validation and reliability of data.

Table 2. Maximum permissible exposure (MPE) values based on international guidelines of IEEE/ICNIRP/ FCC for whole body and localised exposure at 100 kHz to 300 GHz radiofrequency (RF) radiations (≥ 6 min)[3,55].

		Specific Absorption Rate (SAR)	
Exposure Scenario	**Frequency Range**	**Whole-body exposure average SAR (W/kg)***	**Local head/ torso SAR (W/kg)***
Occupational (controlled environment)	100 kHz - 6 GHz >6 GHz -300 GHz	0.4 0.4	10 ----
General Public (uncontrolled environment)	100 kHz - 6 GHz >6 GHz -300 GHz	0.08 0.08	2 ----

"*Whole body average SAR to be averaged over 30 min, Local SAR is to be averaged over a 10 g cubic mass, "---" represents that this cell is not relevant to the basic restrictions."

6. FUTURE PERSPECTIVE

In today's scenario it is almost impossible to avoid exposure from RF-EMF radiations due to their heavy interference and usage in our day-to-day life. However, now it has been felt across the world that along with beneficial perspective they may also have adverse human health endpoints. Therefore, it is required to overcome all the limitations of previous studies and to follow-up suitable standardised methodologies, dose-response studies, assessment procedures to understand the mechanisms of cellular, molecular responses and alteration at genetic level due to RF-EMF radiation exposure.

7. CONCLUSIONS

RF-EMF radiation exposure may elicit different physiological alterations like thermoregulatory responses, modulations in different biological systems like neurological, endocrine, cardiovascular, dermal, ophthalmological, and reproductive along with behavioral responses. These responses have also been reported in various in-vitro, in-vivo, epidemiological and clinical studies; however, it is not clear whether these responses culminate into significant adverse human health consequences. Therefore, a better understanding of the plausible mechanisms of RF-induced biological effects is primarily necessary for determination of potential health hazards, and to develop effective safety measures.

Conflict of Interests: None

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