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Impact of Electromagnetic Fields on Hormonal Integration and DNA Damage with Reference to Breast Cancer Risk-A Review

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Abstract: ***Electromagnetic fields are all around us and everywhere; therefore it is inevitable that everyone is exposed to electromagnetic fields to a certain degree. The widespread use of cell phones has led to cell phone towers being installed indiscriminately. Magnetic fields affect the basic life processes, like growth and development, the structure and function of proteins, lipids, metabolic pathways, antioxidant defense and genetic material. The increasing use of personal computers along with the indiscriminate use of mobiles has provoked public concern about their safety. In the present era of global warming and environmental threats, where various kinds of environmental factors and pollutions are challenging the mankind, the electromagnetic pollution which is of a thermal nature, cannot be neglected. Our awareness of the possible harmful effects of EMFs, especially the cellular phones, is rather recent. Under these circumstances, there is a need for better understanding of the mechanism of action of EMFs with the biological system. Further research using standardized methodology is essential with active support from all concerned, viz. industry, government and philanthropic organizations. Only such an effort can help in formulating suitable guidelines for the use of EMFs.***

Keywords: EMFs, DNA Damage, Melatonin, Estrogen, Breast Cancer

1. Introduction

Life on earth has evolved in a sea of natural electromagnetic (EM) waves. Over the past few decades, this natural environment has sharply changed with introduction of man-made Electromagnetic fields (EMFs). Electromagnetic fields are all around us and everywhere; therefore it is inevitable that everyone is exposed to electromagnetic fields to a certain degree. We need them to see, to listen to radio, to watch television and above all to communicate with mobile phones. The widespread use of cell phones has led to cell phone towers being installed indiscriminately. These towers, also called as base stations, have electronic equipment and antennas that receive and transmit radiofrequency (RF) signals.

Electromagnetic spectrum comprising non-ionizing radiations has a wide range of display. The Extremely low frequency-Electromagnetic fields (ELF - EMFs) i.e., high tension wires, Electrical and electronic gadgets fall in the frequency range between 1 kHz to 300 kHz. The medium frequency radiations i.e., the video display terminals from T.Vs. and personal computers range from 301 kHz to 3000 kHz. The high radiofrequency (RF) fields i.e., the wireless telecommunication system, comprising mobiles and cell towers come in the range of 3001 kHz to 300 GHz.

Magnetic fields affect the basic life processes, like growth and development. Further they are supposed to affect the structure and function of proteins, lipids, metabolic pathways, antioxidant defense and genetic material [1]. The possible association between ELF-EMFs, leukemia and breast cancer has been discussed widely since 1979 [2] particularly when the epidemiological study suggested a possible link between ELF-EMFs and childhood leukemia along with other reports [3], [4], [5] of similar association.

The increasing use of personal computers along with the indiscriminate use of mobiles has provoked public concern about their safety. Scientific research into possible health effects of ELF-EMFs however produced conflicting results and are inconclusive [6]. There are reports showing electromagnetic radiations emitted by electronic gadgets in the environment, during their operation are not strong enough to cause DNA alterations directly [7], [8], [9]. Indirect DNA alterations have been shown through the production of reactive oxygen species [10]. Moreover, *in-vitro* and *in-vivo* studies have demonstrated the ability of electromagnetic fields (EMFs) to cause epigenetic modifications [11]. The mechanism of transcriptional activation/silencing at the chromatin level during exposure to EMFs is reported [12].

Thus the health effects of modulated EMFs have been a subject of debate. However International Association on Research in Cancer (IARC) under aegis of the World Health Organization (WHO) has classified ELFs as a Possible Human Carcinogen in the Group 2B category [13]. Several studies have also reported an association between exposure to ELF-EMFs and neurodegenerative disorders [14], [15], [16], [17]. In the present era of global warming and environmental threats, where various kinds of environmental factors and pollutions are challenging the mankind, the electromagnetic pollution which is of a thermal nature, cannot be neglected. Thus an extensive research is needed to evolve strategies for intervention, to improve health and quality of life with particular reference to electromagnetic radiations.

2. EMFs and Genetic Effects

EMFs are quite pivotal in the electromagnetic spectrum. These waves are common to different types of gadgets, like radar equipment, microwave ovens and cell phones etc. Literature on epidemiological and laboratory studies on their genetic effects is controversial and inconclusive [18],[19]. Genetic effects in the laboratory studies have been conjectured to be thermal [20], [21]. However, a few experiments have shown athermal cellular effects of EMFs [22],[23],[24],[25].

Non- ionizing radiations, like those from microwaves, are considered to be too weak a source of energy to cause any damage at the molecular level. But cellular changes [26]/DNA damage have been reported, which may be indirectly due to signal transduction [27]/ free radical production [28]/ shifts in electrons within DNA molecules [29] and or stress response [30].

2.1 Mechanism of Action

The mechanism responsible for the interaction of EMFs with biological systems is poorly understood. Nevertheless several hypotheses have been proposed in an attempt to understand the phenomenon:

The phenomenon that EMFs affect the ion fluxes through cell membranes by affecting the Na^+K^+ATPase was suggested [31]. Cell membrane receptors have been identified as the primary sites in detecting and transducing amplitude modulated component of radiofrequency EMFs [27], [30]. Magnetic fields due to EMFs are too weak to cause any damage at the molecular level. However, the magnetic fields can interact with conducting electrons in the stacked bases of the DNA [30]. Such interaction may alter the gene function by altering the conformation of the DNA. The concept that magnetic field can affect post-translational modification of proteins, such as poly-ADP ribosylation by epigenetic mechanism was reported [32]. These effects are highly specific for both the cell type and the magnitude and frequency of the applied magnetic field. A proposal that free radicals play a role in magnetic field induced DNA damage was inferred [33]. EMFs may evoke stress response in cells. This stress response acts through the so called heat shock proteins (HSPs) and is essential for normal cellular function. HSPs act as “molecular chaperons”, binding to and stabilizing partially unfolded proteins, thus providing the cell with protection from imposed environmental stress.

At lower levels, a partial unfolding of specific target proteins occurs which will be insufficient to induce the stress response, but sufficient to alter protein function. At higher levels a more unfolded conformation is induced. The stress response will be activated, protecting the protein, and preventing an observable biological effect. At very high levels, protein aggregation and precipitation occurs, and despite the activation of the entire stress response, a catastrophic biological effect will be observed like DNA damage [34]. It has also been emphasized that the cellular stress response elicited by athermic electromagnetic fields appears to differ from the thermic HSP induction. These stressors are thought to act on different molecular targets [30], [35].

Several breast cancer studies including metanalysis have generated a large number of arrays with complex genomic data with efforts to compare the prognostic performance of the intrinsic subtypes and four signatures in one data set [36]. However, the studies could not provide a biological rationale for the findings.

3. Mobile Phones, Cell Towers and Health Effects

Mobile telephony, the integral unit of modern telecommunication and third generation wireless technology, relays information with radiofrequency (RF) signals. The Indian Telecommunication network has grown exponentially and presently it is the second largest in the world after China. The number of telephone subscribers in India increased from 915.19 million at the end of September-2013 to 933.02 million at the end of March-2014. The overall Tele-density in India also increased from 74.02 as on 31st December, 2013 to 75.23 by 31st March, 2014 and Cell Towers have gone up to 5,93,601 lakh [37]. There is still ongoing controversy and uncertainty whether the radiofrequencies generated by mobile phones and base station antennas have any biological effect, particularly on DNA integrity, epigenetic alterations/methylation and Gene expression in human subjects living or working in the vicinity of Cell Towers [38], [39].

4. Melatonin in Pathogenesis and Therapy of Cancer

Melatonin is a neuroendocrine hormone, an indoleamine (N-acetyl-5 methoxytryptamine) secreted by the pinealocytes of the pineal gland situated in the hypothalamic region of the brain. It transduces the body’s circadian rhythms and controls the sleep-wake cycle, an internal 24 hour time keeping system (biological clock) [40]. Melatonin’s hypothermic; antioxidant and free radical scavenging properties attribute it to an immune modulator and an oncostatic agent. Altered patterns and/or levels of melatonin secretion have been reported to coincide with sleep disorders, jetlag, depression, stress, immunological disorders and some types of cancers. [41], [42], [43]. Lately, the physiological and pathological role of melatonin has become a priority area of investigation, particularly in breast cancer, melanoma, colon cancer, lung cancer and leukemia [44], [45]. According to the ‘melatonin hypothesis’ of cancer, [46] ,[47] the exposure to light at night (LAN) and anthropogenic electric and magnetic fields is related to the increased incidence of breast cancer due to melatonin disruption [48]. Many clinical studies have envisaged the potential therapeutic role of melatonin in various pathophysiological disorders of cancer [49]. Melatonin is supposed to reduce toxicity after chemotherapy, radiotherapy, immune-hormonal therapy and surgery. A substantial reduction in risk of death and low adverse effects were reported from various randomized controlled trials of melatonin treatment as an adjuvant therapy in cancer patients [40].

5. Melatonin, EMFs, LAN and Breast Cancer

Breast cancer is the most common cancer among women in the developed countries probably due to the pervasive use of electric power and exposure to light at night (LAN). It is the second leading cause of cancer death in women, after lung cancer [50]. ELF-EMFs and LAN are hypothesized to be responsible for the changes in hormonal configurations leading to development of cancer, particularly in occupationally exposed women. Stevens [47] suggested that ELF-EMFs and visible light at night (around 1015 Hz) may increase the long term risk of breast cancer [51].

Light of sufficient intensity, duration and spectral quality suppresses melatonin production at night. The epidemiological studies provided evidence about the potential risk factor of LAN in breast cancer with its involvement in the entire circadian axis rather than just melatonin depression [52], [53], [54], [55].

Although the effect of EMF on melatonin release was extensively studied, the site and mechanism of action that leads to changes in melatonin synthesis is unclear. The effect of magnetic field on melatonin synthesis can result from changes in neural input, at the level of the retina and the suprachiasmatic nuclei [56]. Magnetic fields are perceived and interpreted by photoreceptors in eye as “light”, suppressing melatonin levels. Magnetic fields reduce the activity of the rate-limiting enzyme, N-acetyltransferase (NAT) in melatonin production and inhibit the activity of melatonin synthesizing enzyme, hydroxy-indole-O-methyltransferase (HIOMT) [57]. The free radicals generated by magnetic fields are scavenged by melatonin and due to its more rapid scavenging, there is a decline in melatonin levels. Therefore melatonin suppression maybe due to the interference of ELF-EMFs and LAN during its synthesis and its scavenging activity with the free radicals [58].

Hence studies have to be taken up to understand the plausible biological mechanism underlying the effect ELF-EMFs, LAN and reduced nocturnal melatonin which is supposed to be an oncostatic component [40].

6. Melatonin, Estrogen - EMFs and Breast Cancer

Melatonin levels are believed to be inversely related to estrogen levels. For example, when melatonin levels are low, estrogen levels are believed to be high, and vice-versa. Therefore, if ELF – EMFs and LAN suppress the normal nocturnal rise in melatonin, estrogen levels would subsequently be increased. Because increased levels of estrogen are hypothesized to increase the risk of breast cancer, the suppression of melatonin by magnetic fields possibly could increase the risk of breast cancer. [59], [60], [61], [62].

Estrogen is a steroid hormone that is necessary for the normal development and growth of the breasts, menstrual cycle and reproductive organs essential for perpetuation of species [63], [64], [65]. Estrogen may be implicated in breast cancer risk because of its role in stimulating breast cell division during the critical periods of breast growth and development [66], [67], [68], [69]. A woman's risk for breast cancer is associated with increased levels of estrogen. Women with high levels of estrogen are believed to be at higher risk of breast cancer. It is important to understand how lifestyle and environmental factors may affect the increased levels of estrogen. Such environmental factors could be ELF-EMFs and LAN [70].

There is mounting evidence of an association between night shift work and breast cancer risk. A study [71] explained about two interrelated mechanisms by which night shift work is associated with breast cancer risk. Accordingly melatonin acts as a chemical code for the night; the longer the night, longer the duration of secretion. Melatonin appears to be involved in the regulation of the release of gonadotropins (LH and FSH) from the pituitary stimulating estrogen production and release. However this study concluded that though reproductive hormones like LH and FSH were modestly increased in the night shift workers and estrogen levels were not. The findings do not support the mechanism by which the night shift work could increase breast cancer risk through increased levels of reproductive hormones including estrogen. A more direct mechanism where ELF-EMFs and LAN exposure could increase cancer risk lies in the oncostatic property of melatonin and its circulating levels [72], [73], [61], [39].

7. Conclusion

With industrial revolution, our exposure to EMFs, even at power line frequencies, as well as chemical pollutants has increased considerably. There is every possibility of synergistic effects of EMFs with other pollutants. Biological systems are highly complex and it is unlikely that a single mechanism could explain the effects of EMFs on them. It is reasonable to expect that more than one interaction may be responsible for their biological effects.

Cancer has a long incubation period which may be sometimes 20 years. However, certain cellular changes, like DNA damage serve as biomarkers for its future occurrence. For example, in our lab we carried out studies on the effects of low-level, low-frequency electromagnetic fields on human white blood cells using comet assay . We have not only seen a significant increase in DNA damage in these cells as compared to the controls, but also a dose response relationship [74], [75].

Most of the epidemiologic and laboratory findings do not provide strong support for an association between EMF and cancer. The limited statistical data as well as bias present in the existing literature does not rule out a relationship between EMF and cancer. However given the ubiquitous nature of EMF exposure, and especially the high incidence of breast cancer in the industrialized countries, even a small risk will potentially have a substantial public health impact. A preliminary warning has already been given by the Working Group of the National Institute of Environmental Health Sciences of the USA (NIEHS) and The International Agency for Research on Cancer (IARC) a part of World health organization (WHO) has concluded that extremely

low frequency EMF is a class 2B (possible) human carcinogen [13].

Our awareness of the possible harmful effects of EMFs, especially the cellular phones, is rather recent. Although we may not be able to come to a conclusion on the health hazards of EMFs interacting with physical/chemical and/or biological agents, we cannot completely rule out the possibility. Under these circumstances, there is a need for better understanding of the mechanism of action of EMFs with the biological system. Further research using standardized methodology is essential with active support from all concerned, viz. industry, government and philanthropic organizations. Only such an effort can help in formulating suitable guidelines for the use of EMFs. A line should be drawn between use and abuse until a "clean chit" is issued.

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