Environmental Research xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

# The genomic effects of cell phone exposure on the reproductive system

Ahmad Yahyazadeh[a], Ömür Gülsüm Deniz[a], Arife Ahsen Kaplan[a], Gamze Altun[a], Kıymet Kübra Yurt[a,*], Devra Davis[b]

[a] Department of Histology and Embryology, Medical Faculty, Ondokuz Mayıs University, 55139, Samsun, Turkey
[b] Environmental Health Trust, P.O. Box 58, Teton Village, WY 83025, United States

ARTICLE INFO

*Keywords:*
Electromagnetic field
Genotoxicity
DNA damage
Fertility

ABSTRACT

Humans are exposed to increasing levels of electromagnetic fields (EMF) at various frequencies as technology advances. In this context, improving understanding of the biological effects of EMF remains an important, high priority issue. Although a number of studies in this issue and elsewhere have focused on the mechanisms of the oxidative stress caused by EMF, the precise understanding of the processes involved remains to be elucidated. Due to unclear results among the studies, the issue of EMF exposure in the literature should be evaluated at the genomic level on the reproductive system. Based on this requirement, a detail review of recently published studies is necessary. The main objectives of this study are to show differences between negative and positive effect of EMF on the reproductive system of animal and human. Extensive review of literature has been made based on well known data bases like Web of Science, PubMed, MEDLINE, Google Scholar, Science Direct, Scopus. This paper reviews the current literature and is intended to contribute to a better understanding of the genotoxic effects of EMF emitted from mobile phones and wireless systems on the human reproductive system, especially on fertility. The current literature reveals that mobile phones can affect cellular functions via non-thermal effects. Although the cellular targets of global system for mobile communications (GSM)-modulated EMF are associated with the cell membrane, the subject is still controversial. Studies regarding the genotoxic effects of EMF have generally focused on DNA damage. Possible mechanisms are related to ROS formation due to oxidative stress. EMF increases ROS production by enhancing the activity of nicotinamide adenine dinucleotide (NADH) oxidase in the cell membrane. Further detailed studies are needed to elucidate DNA damage mechanisms and apoptotic pathways during oogenesis and spermatogenesis in germ cells exposed to EMF.

## 1. The molecular nature of the genetic material and genotoxicity: a general overview

DNA integrity is of the utmost importance for the cell. Genotoxicity encompasses damage to genetic material such as DNA fragments, gene mutations, chromosomal abnormalities, clastogenicity and aneuploidy, which occur in the nucleus, chromosome and DNA architecture. Genotoxicity studies examine the changes that take place in the DNA molecules of cells during the normal biological processes of the organism or due to chemical, physical and biological factors (Mortelmans and Rupa, 2004; Young, 2002). DNA damage derived from the interaction of genotoxic agents with enzymes causing the replication of the DNA or genome and mutation is also defined as a genotoxic effect (Mortelmans and Rupa, 2004; Young, 2002; Zeiger, 2004). Disorders in the substantial molecules and pathways involved in DNA damage lead to tissue damage, cancer, infertility and some genetic and multifactorial diseases (Kirsch-Volders et al., 2003; Mateuca et al., 2006).

## 2. The role of the electromagnetic field in genotoxicity

The widespread use of mobile phones often kept in close proximity to the gonads raises important questions about their potential effects on human reproduction (Merhi, 2012). The interaction of electromagnetic fields (EMF) with biological tissues depends on various physical, biological and environmental factors. To date, investigation of the genotoxic effect of EMF exposure has been largely carried out in vitro under short-term exposure conditions, although some in vivo studies have been conducted (Seyhan and Canseven, 2006). EMF is known to cause

*Abbreviations:* EMF, electromagnetic field; NADH, nicotinamide adenine dinucleotide; ROS, reactive oxygen species; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; RNS, reactive nitrogen species; TNF, tumour necrosis factor; PKC, protein kinase C; DR, death receptor; TNFR, TNF receptor; TRAIL, TNF-related apoptosis inducing ligand; Apaf-1, apoptosis protease activating factor-1; MAP, mitogen-activated protein, Fas fatty acid synthase; 4HNE, 4-hydroxynoneNal; ETC, electron transport chain; GSM, global system for mobile communications; SAR, specific absorption rate

* Corresponding author.
*E-mail address:* kiymet.yurt@omu.edu.tr (K.K. Yurt).

https://doi.org/10.1016/j.envres.2018.05.017
Received 20 October 2017; Received in revised form 11 May 2018; Accepted 13 May 2018

**Table 1**
Summary of the genomic effects of mobile phones on reproductivity.

| Frequency | Study type | Dose/duration | Conclusion/mechanism | References |
|---|---|---|---|---|
| 900 MHz RF/MW | Rats | 1 h /7 days | Long-term exposure to cellular phone radiation cause hypospermatogenesis and increased the PCNA activity in the testis. | (Bin-Meferij and El-Kott, 2015) |
| 1.8 GHz RF-EMF | Human | Multiple measurements from 15 to 120 s | RF-EMR induced the damage in the DNA and sperm function through the leakage of electrons from the mitochondria and oxidative stress. | (De Iuliis et al., 2009a) |
| 875 MHz EMF | Cell culture (HelA and Rat 1 cells) | 10 min | ERKs are rapidly activated against mobile phone irradiation at different intensities. In addition, MAPK activation is important in the molecular mechanism for electromagnetic-irradiation. | (Friedman et al., 2007a) |
| 900/1800 MHz EMF | Human | Long-term | Direct exposure to long-term mobile phone exposure causes sperm DNA fragmentation. | (Gorpinchenko et al., 2014) |
| 848.5 MHz RF | Rat | 12 weeks | Exposure to RF-EMF did not affect molecular events in testicular functions and did not lead to apoptosis induction and expression of caspase 3, Bcl2, or p53. | (Lee et al., 2010) |
| 1800 MHz EMF | Cell culture (mouse spermatocyte-derived GC-2 cell) | 24 h | Long-term use of mobile phones induced the accumulation of damaged DNA. Potential preventing effects of antioxidants against genotoxicity can be considered in this context. | (Liu et al., 2013) |
| 1800 MHz EMF | *Drosophila melanogaster* | 30 min | Pulsed radiation induced cytopathic mechanisms and altered genetic programs in the ovaries of *D. melanogaster*. | (Manta et al., 2017) |
| 1.88–1.90 GHz EMF | *Drosophila melanogaster* | < 0.5 – 1 h > 6, 24, 96 h | RF exposure may not be directly related to oxidative stress caused by radiation. | (Manta et al., 2014) |
| 900/1800 MHz, 1880/1900 MHz, 2.44 GHz, 92.8 MHz, 27.15 MHz | *Drosophila melanogaster* and *Drosophila virilis* | 6 min and 12 min | This study is important in showing the effects of EMF at different frequencies. All EMF sources affected apoptosis induction, even though they were at very low intensity levels. | (Margaritis et al., 2014b) |

alterations in biological functions through thermal and non-thermal (chemical) effects on tissues (Tumkaya et al., 2016). If EMF application is sufficient to cause heat in biological architectures, this will result in a temperature rise in the tissue, followed by biological changes deriving from that thermal increase (thermal effects). Depending on the increase in temperature, cells may die or mutagenesis may occur. If the applied EMF does not have a heat enhancing effect but causes a biological alteration, these effects are defined as non-thermal (Repacholi, 1998).

Many experiments have been performed to investigate health problems in humans exposed to EMF. Reports have asserted that EMF has genotoxic effects on DNA (see Table 1). In contrast, some empirical studies have reported that EMF does not result in DNA damage, genetic disturbances, or inherited effects (Mooney et al., 1999). Studies performed in recent years have reported that EMF exposure can cause male and female infertility by triggering morphological and functional alterations in the reproduction system. Despite the considerable previous research about the effects of EMF on the male reproductive system, there has been scarcely investigation of the female reproductive system, particularly in terms of DNA damage. EMF radiation has been reported to damage DNA in reproductive organs (De Iuliis et al., 2009a; Panagopoulos et al., 2010). EMF influences the proliferation, differentiation and apoptotic processes of the cell by altering cellular membrane functions and gene expression (Desai et al., 2009; Lin, 1997; Zalata et al., 2015). In addition, EMF at different frequency ranges can stimulate biological responses to proliferation, mitochondria, cell death, apoptotic pathways, heat shock protein, cell differentiation, the structure-function of the cell membrane, and free radical metabolism, as well as DNA breakage (Blank, 2005; Capri et al., 2004; Cleary et al., 1996; Lai and Singh, 1996; Lantow et al., 2006; Leszczynski et al., 2002; Lixia et al., 2006; McNamee et al., 2003; Moustafa et al., 2004). One study reported that continuous exposure to a 1800 MHz frequency (cell phone radiation with 1, 2 and 2 W/kg specific absorption rate (SAR) values for 5 min on, 10 min off, on human and rat cell cultures for 4, 16, and 24 h) resulted in an increase of single and double strand breaks for all exposures after 16 h (Diem et al., 2005).

The main mechanism of EMF effects emitted from cell phones involves the impact on the mitochondria, apoptotic pathways, heat shock proteins, free radicals metabolism, cell proliferation and differentiation, DNA damage and plasma membrane destruction (Phillips et al., 2009). Blank and Goodman (1997) reported direct interaction between EMF and DNA (Blank and Goodman, 1997). Furthermore, the use of mobile phones has been reported to create oxidative stress and thus increase the risk of cancer (Moustafa et al., 2001). Although some of the cellular mechanism associated with the impact of EMF on reproductive genotoxicity is known but it seems that pathway based researches for examining the effect of EMF on the cells, organs and system are needed.

## 3. Effects of electromagnetic fields and DNA damage: responses to oxidative stress

It has been shown that the production of free oxygen radicals by EMF leads to the formation of reactive oxygen species (ROS) and that lipid peroxidation causes cell damage and programmed cell death (Moustafa et al., 2004) (Fig. 1). Studies have revealed that EMF increases the formation of free radicals, one of the external factors that cause oxidative stress. A defence mechanism in antioxidants for preventing ROS formation and their damage has been highlighted in the literature (Hanukoglu, 2006). In addition to the formation of free radicals as a side-product of normal metabolism, environmental toxic factors, such as exposure to EMF, ionizing radiation and heat can also produce these (Bin-Meferij and El-Kott, 2015; Saunders and Kowalczuk, 1981). If the rate of formation of free radicals and the rate of their removal in the organism is in equilibrium, this is known as the oxidative balance. Impairment of the oxidative balance results in oxidative stress, lipid peroxidation and the formation of ROS.

Although DNA is a stable molecule, it can interact with free radicals