REVIEW

THE HISTOPATHOLOGICAL CHANGES INDUCED BY ELECTROMAGNETIC RADIATION (EMR) ON THE NERVOUS TISSUE

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ABSTRACT

Electromagnetic radiation (EMR) has attracted the attention of scientists worldwide and, following the development of modern technology, it became a daily presence. Over the past years, a series of authorised institutions, including the World Health Organisation (WHO), have been focused on investigating the effects of EMR on human health. One of the major impacts of EMR in modern life concerns its potential carcinogenic effect, as it is well known that radiation interferes with oxidative stress and its signalling pathways. Despite the fact that EMR exposure is tightly linked to the occurrence of toxicological, genotoxic and carcinogenic effects, and testicular alterations, current literature data does not provide any certain evidence regarding the relation between electromagnetism (EM) and cancer. A particular category of radiofrequency electromagnetic (RF-EM) based gadgets that currently have a wide usage especially amongst the young population are mobile phones. Due to electromagnetic field (EMF) generation, mobile phones induce physiological and morphological changes in living organisms, the influences of RF-EM being demonstrated in plants of common usage. Despite the continuous efforts to obtain accurate measurements of EM effects on human health, the results remain unconvincing. The influences of RF field exposure from mobile phones shows an increased variability regarding brain tumours development. This review aims to collect and interpret some of the most representative publications that have been focused on obtaining valuable information regarding the impact of EMR on human health and, especially on the nervous tissue.

Keywords: electromagnetic radiation (EMR), radiofrequency electromagnetic (RF-EM), mobile phones, nervous tissue, histopathological changes, brain tumours

EMR AND HUMAN HEALTH: UNCERTAIN AND CONTROVERSIAL ISSUES

Ever since its discovery dating back two centuries ago, EMR has attracted the attention of scientists worldwide and, following the development of modern technology, it became a daily presence. One of the major impacts of EMR in modern life concerns its potential carcinogenic effect (1), as it is well known that radiation interferes with oxidative stress and its signalling pathways (2). RF radiation has been shown to promote stem cells impairment resulting in differentiation and self-renewal (3). The effects of EMR on living beings may or may not generate clinical changes and can be either reversible or irreversible, when permanent biological changes occur (3, 4).

A reduction in the amount of protein compounds following RF and microwave food treatment has been shown by Zhong et al. in a study conducted on black soybeans (5). However, their results are controversial due to the minimal increase in the proportion of essential amino acids (5). Other controversial results regarding the effects of EM were obtained in 2008, when Yao et al. (6) demonstrated the beneficial effects of EM noise in blocking DNA damage and RF-induced intracellular reactive oxygen species formation (6). A particular category of RF-EM based gadgets that currently have a wide usage especially amongst the young population are mobile phones (7-9). Due to EMR generation, mobile phones induce physiological and morphological changes in living organisms, the influences of RF-EM being demonstrated in plants of common usage (10). In a recent study, Halgamuge (10) demonstrated the existence of a differentiated sensitivity of plants towards weak RF radiation exposure, however, the results of this study are not associated with the impact of EM on humans. Since 1999, a series of authorised institutions, including the World Health Organisation, have been focused on investigating the effects of EMR on human health (11). Despite the fact that EMR exposure is tightly linked to the occurrence of toxicological, genotoxic and carcinogenic effects, and testicular alterations (11,

12), current literature data does not provide any certain evidences regarding the relation between EM and cancer (11, 13). The attempt to elucidate the biological changes induced by EMR in humans has gone so far that in 2015, Roser et al. (14) designed an integrative exposure surrogate that combines near-field and far-field RF-EMR exposure in a single brain and whole-body exposure measure (14). Despite the continuous efforts to obtain accurate measurements of EM effects on human health, the results remain unconvincing. The influence of RF field exposure from mobile phones shows an increased variability regarding brain tumour development (15).

ARE MOBILE PHONES A THREAT FOR THE NERVOUS TISSUE?

In a review published in 2015, Redlarski et al. stated that "the harm caused by this pollution [EMR] is still open to questions since there is no clear and definitive evidence of its negative influence on humans" (1). High intensity magnetic field exposure has been reported as being responsible for the increased risk of developing tumour lesions (1). Starting from the late '70s it has been shown that EMR determines an increase in the incidence of leukaemia and different brain tumours, but the results were highly variable amongst different countries and even within the same geographic region (16-19). Unlike the study conducted by Wertheimer and Leeper (17) in 1979, where the influence of EMR on human malignancies was highlighted, in the late '80s, Savitz et al. (20) found no significant correlations between magnetic field exposure and cancer development. Despite the contradictory results obtained over the past years related to whether or not mobile phones exert a negative impact on human biological systems, several studies pinpoint an increased risk of developing brain tumours following long term RF exposure (21,22). Due to the proximity to the radiation device, a large amount of EM energy is absorbed in the nervous tissue, thus transforming mobile phones into potential tumorigenic factors (21). A number of case-control studies conducted between 1994 and 2000 that were focused on the potential risk of mobile phones in the occurrence of tumour lesions such as acoustic neuromas and gliomas found no direct impact of EM device usage on the nervous tissue (23-25). However, in case of brain tumours that develop in the occipital, temporal and temporoparietal lobes, an increased risk was found for ipsilateral mobile phone usage (21). Despite the fact that the molecular mechanisms through which EMR determines tumorigenic changes in the nervous tissue are currently incompletely elucidated, it is assumed that reactive oxygen species are among the key players that enhance microwave radiation effects resulting in neurodegenerative lesions (22). Also, up to this point, the time interval between cellular phone usage and tumour development, has not been clearly established, however, long-term exposure is considered an important risk factor (22), especially when implying at least ten years of exposure (24).

According to Hardell et al. (21), acoustic neuromas may be regarded as "marker" tumours indicating an increased risk for brain tumour development following EMR exposure due to their particular location in anatomical areas that are subject to high radiation absorbance during mobile phone calls (21). Unlike the previously mentioned studies, the results obtained by Takebayashi et al. (26), found no statistically significant correlations between mobile phone calls and acoustic neuroma risk, thus the interpretation of these lesions as "signal" tumour types (21) is controversial. Despite the existence of positive results regarding the association between mobile phone exposure and acoustic neuroma development, meningioma occurrence in long-term mobile phone users is either absent or less likely, even for over ten years of usage (27-29). These differential effects determined by EMR are partially due to its variability in terms of intensity, frequency, duration and modulation mode, and depend on the characteristics of the cell microenvironment (30).

NERVOUS TISSUE CHANGES FOLLOWING EMR EXPOSURE

Despite the common involvement of the reproductive, cardiovascular and hematopoietic systems in different lesions caused by EMR, the central nervous system exhibits the most increased sensitivity due to the earlier and more severe ultrastructural disruption occurring in the neurons (30). This disruption is mostly related to mitochondrial injuries that affect ATP stores resulting in structural nervous tissue damage (30). The structural changes that occur following EMR exposure are more evident in the brain and are associated to brain disfunction with clinical manifestations such as symptoms of neurasthenia (30). The occurrence of neurodegenerative lesions implies the interference of EMR with acetylcholinesterase activity (31), however, oxidative damage in neurons was found under particular circumstances and neurotoxic effects were differential and location-dependent (32). Glutamate, beta-amyloid and hydrogen peroxide are well documented neurotoxic agents, however, cooperative effects with EMR were found only for hydrogen peroxide affecting cholinergic cells but not primary cortical neurons (32). Moreover, RF exposure results in more severe effects in case of stem cells than in case of mature cells, as stem cells present a more increased sensitivity towards external stimuli and EMR affects crucial cell processes such as differentiation, migration and proliferation (30).

It has been shown that cognitive damage is a result of long-term EM exposure due to increased β-amyloid depositions in the neurons from the hippocampus (33). Moreover, following EMR exposure, hippocampal neurons show increased oxidative stress and accumulate several neurodegeneration-associated proteins (33). Based on an in vitro model that used spiral ganglion neurons obtained from neonatal rats, Zuo et al. (34) showed that short-term RF-EM exposure induces ultrastructural changes in the nervous cells that were previously subject to damages via lipopolysaccharide-induced inflammatory reactions (34). Additionally, the study conducted by Tan et al. (35) showed the existence of microstructural changes in the rat hippocampus caused by microwave exposure. Although presenting regional heterogeneity, different cell injuries such as irregular arrangements, karyopyknosis, oedema and broadening cellular space, are responsible for the cognitive damages (35). Microwave radiation effects were also found at an ultrastructural level, consisting in severe neuronal damages including mitochondrial swelling and ridge rupture, cavitation, endoplasmic reticulum swelling along with a reduction in the amount of Nissl bodies, and cytoplasmic relaxation (35). Nuclear injuries that are commonly regarded as irreversible, are mostly represented by chromatin concentration and migration as well as by the broadening of the nuclear membrane gap in case of microwave exposure (35). The degree of reduction in the amount of Nissl bodies is strongly related to the microwave power density resulting in a disruption of protein synthesis (35). Thus, according to Tan et al. (35), the morphological changes that occur in the hippocampal neurons are responsible for the behavioural degeneration and for the disturbances in the cerebral electrophysiological pattern, the molecular basis of these lesions being represented by an abnormal energy metabolism (35).

FUTURE CHALLENGES

Current literature data regarding the potential implications of EMR in inducing histopathological changes of the nervous tissue are controversial and mobile phones involvement in the occurrence of brain tumours is incompletely elucidated. However, several studies report the existence of degenerative morphological and ultrastructural features following EMR exposure in relation to cognitive deficiency (35). Despite the fact that the histopathological effects of EMR leading to cognitive loss have been demonstrated in studies that used rat experimental models, the literature data provides a number of publications that are focused on the effects of extensive mobile phone usage in the young human population. According to Abramson et al. (36), EMR generated by mobile phones is associated with an increase in rapidity and a decrease in accuracy in case of high-level cognitive tasks. It appears that the cognitive changes in adolescents who commonly use mobile phones as communication means are related to increased exposure to EMR (37, 38). Contrary to these results, Schoeni et al. (39) showed that memory performance in adolescents is negatively associated with the cumulative duration of mobile phone usage but positively related to RF-EM field dose. Unlike the previously mentioned studies, Bhatt et al. (40) found a limited association between the use of mobile phones in primary school children and changes in their cognitive function. Anyway, the variability of cohorts used in these studies is too large to allow definitive conclusions.

Recent studies however, support the existence of three population exposure categories in modern daily life, namely intermittent variable partial body exposure and whole-body low-level exposure, either intermittent variable or continuous (41). In relation to these facts, Thielens et al. (42) evaluated a number of microenvironments located in developed countries and demonstrated the existence of moderate to high correlations in case of body and head exposures to RF-EMR field. The relation between mobile phone usage and brain tumours remains inconsistent as contradictory. Thus, in order to increase result representativeness and generalizability regarding the implications of EMR as a potential brain tumour risk factor, the MOBI-Kids study includes large sample size group from several countries where mobile phones are widely used amongst children (43). However, further attempts are needed in order to establish whether or not mobile phones have direct implications in the occurrence of either benign or malignant lesions of the nervous tissue.

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