Review article

Skeptical approaches concerning the effect of exposure to electromagnetic fields on brain hormones and enzyme activities

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A B S T R A C T

This review discusses the effects of various frequencies of electromagnetic fields (EMF) on brain hormones and enzyme activity. In this context, the mechanism underlying the effects of EMF exposure on tissues generally and cellular pathway specifically has been discussed. The cell membrane plays important roles in mediating enzymatic activities as to response and reacts with extracellular environment. Alterations in the calcium signaling pathways in the cell membrane are activated in response to the effects of EMF exposure. Experimental and epidemiological studies have demonstrated that no changes occur in serum prolactin levels in humans following short-term exposure to 900 Mega Hertz (MHz) EMF emitted by mobile phones. The effects of EMF on melatonin and its metabolite, 6-sulfatoxymelatonin, in humans have also been investigated in the clinical studies to show a disturbance in metabolic activity of melatonin. In addition, although 900 MHz EMF effects on NF-κB inflammation, its effects on NF-κB are not clear.

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1. Introduction

This study reviews the effects of exposure to various frequencies of electromagnetic fields (EMF) on brain hormones and enzyme activity. The increasing use of electronic and electric devices such as televisions, personal computers, radios, and mobile phones increased human exposure to extremely low frequency electromagnetic fields (ELF-EMFs) emitted from power lines and power cables. The global biological impact of radiation resulting from EMF exposure on environmental pollution and attendant health risks as our life style changes has become an important issue for public health services and environmental organizations such as World Health Organization and Environmental Health Trust. Exposure to electric fields disturbs brain functions, hormones and enzyme activity, depending on the frequency and duration of that exposure. The biological dangers posed by EMF exposure and threats to human safety at home and work have become important issues in this century [1–3].

Radiofrequency (RF) fields (0.5 MHz–100 GHz) are emitted from radar tracking, wireless communication devices, mobile phones and magnetic resonance imaging (MRI) equipment. Some industrial processes also create static magnetic fields. While EMF is considered a common environmental presence in the modern world, ELF-EMF is a product of electricity generation [4]. External EMF can alter biological functions by inducing electric fields in living organisms. Diseases such as leukemia in children and brain cancer in adults, Lou Gehrig’s disease, depression, suicide, and Alzheimer’s disease may be related to EMF exposure [1].

The present review focuses on the enzymatic and hormonal changes, during the EMF exposure and underlying cellular mechanisms.

2. Mechanisms of the effects of EMF

The biological effects of EMF are associated with the induction of electric fields in the body. Strong electric fields lead to damage to neuronal functions, depending on the frequency involved. The thermal effects of EMF are associated with energy absorption that
results in the oscillation of molecules [3]. In this context, understanding the effects of EMF on biological systems is important in order to identify protective mechanisms against EMF exposure [5].

The magnitude of the photon energy of radiofrequency EMF (RF-EMF) is one-millionth of the ionization energy and one-thousandth of the thermal energy. However, non-thermal effects on biological systems of RF-EMF at low levels are controversial. The photon energy of EMF emitted from mobile phone breaks the weak non-covalent bonds of DNA strands and induces chemical reactions and changes. Several potential reaction mechanisms have been reported [6,7] such as oscillating resonances, reactive oxygen species (ROS)-mediated mechanisms, which induced dipole moments [8].

2.1. Cellular response to EMF exposure: signaling pathways

Understanding the underlying mechanisms of EMF effects on tissues is important for determining the targets of EMF in cells. Alterations in the calcium signaling pathways have been reported in response to the effects of EMF exposure, calcium channels and receptors on the cell membrane, which affects the response of mitochondrial calcium reaction as the energy source of the cell [9]. Additionally, there is an increase in intracellular Ca²⁺ levels as a result of the cellular effects of EMF exposure. Alterations in voltage-gated calcium channels (VGCCs) have been investigated, and studies have shown enhanced activity of VGCCs due to direct effects of EMF exposure in many cell types [10–12]. In particular, VGCCs play a crucial role in the response to ELF-EMF [13]. In the microwave, EMF activation of VGCCs causes a rapid increase in intracellular Ca²⁺, nitric oxide, and peroxynitrite. While the pathophysiological effects of EMF are related to the Ca²⁺/nitric oxide/peroxynitrite pathway at the cellular level, its therapeutic effects are related to the Ca²⁺/nitric oxide/cGMP/protein kinase G pathway [14]. Animal studies have suggested the effects of RF-EMF on the calcium efflux and influx in the neurons [15–17]. However, the results regarding the effects of RF-EMF on the VGCCs are still unclear. In addition, Platano et al. have evaluated the Ba²⁺ currents through VGCCs after continuously wave of 900 MHz EMF. In this study, there was no effect of acute exposure to GSM modulated 900 MHz EMF VCCG in the rat cortical neurons [18]. In this regard, it is needed new experimental studies to be made by various duration and dose of EMF exposure to see exact effects of EMF on the VGCCs.

The mitogen-activated phosphokinase (MAPK) family plays a key role in the response to tissue damage by controlling cell proliferation and metabolism. The phosphorylation of transcription factors occurs by activation of the MAPK cascades 1 pathway [19]. Low concentrations of free radicals can stimulate the proliferation and survival of different cell types. The effects on cell proliferation of ROS, which play a key role as a secondary messenger in the physiological process, can thus be reported (Fig. 1). The secondary messenger role of ROS is very important for regulation of cytosolic Ca²⁺ concentrations. The level of cytosolic Ca²⁺ regulates the protein phosphorylation and activation of the AP-1 family factors and nuclear factor kappa B (NF-κB) [13]. Activation of the protein kinases pathways regulates the physiological response to EMF exposure. Activation of the ERK signaling cascade results from the intracytoplasmic effect of EMF. In addition, an increase in ROS levels stimulates the matrix metalloproteinases, and activation of the extracellular signal-regulated kinase (ERK-1/2) cascade then occurs [14].

2.2. The effect of EMF on NF-κB

The effect of EMF on inflammation is undeniable. In this context, some studies have focused on the effects of EMF on the inflammatory process and especially the regulatory effect of NF-κB in the immune system [19,21]. Lee et al. investigated the effects of exposure to 900-MHz EMF on the activation of the Jun N-terminal kinases (JNK) apoptosis signaling pathways by raising ROS levels in Drosophila [20]. Although the role of JNK in apoptosis is unclear, the balance between JNK and NF-κB controls cell death and survival [22–24]. Furthermore, the role of NF-κB in cell survival and death is related to the prevention of JNK activation [25]. NF-κB regulates JNK activity and therefore regulates programmed cell death through interaction with ROS, JNK, and caspases. In this context, mitochondrial superoxide dismutase (SOD), known as manganese-dependent SOD (MnSOD), an antioxidant enzyme, is regulated by NF-κB. ROS-mediated mitochondrial damage and apoptosis occur by accumulation of O₂⁻ following inhibition of SOD (Fig. 2) [26]. It should also be noted that NF-κB plays a crucial role in the immune response as a source of tumor growth factors [27]. However, the effects of exposure to 900-MHz EMF on NF-κB and the mechanisms involved are unclear.

3. Effect of EMF on enzymatic activity

The health hazards posed by ELF-EMFs emitted from power lines, domestic wiring and power cables are controversial. The antioxidant effect of melatonin in experimental exposure to ELF-EMF radiation is not well established [28]. The alteration or suppression of melatonin is correlated with various physiological disturbances such as sleep disorders, depression, stress, breast cancers, melanoma, colon cancer, lung cancer and leukemia [29]. The alteration or suppression of melatonin is correlated with various physiological disturbances such as sleep disorders, depression, stress and cancers [30]. However, one scientific report suggested that melatonin suppression might be responsible for various biological effects due to the effect of EMF [31]. A comprehensive
investigation of health threats in humans exposed to ELF-EMF is now required as a matter of urgency [32].

The applied EMF affects membrane-bound enzyme activity, but this effect on soluble isomers of adenylyl kinase is negligible. ELF-EMF has been reported to affect the activities of soluble enzymes [30,33]. These findings indicate that the membrane may play a key role in mediating the effect of the field on enzymatic activity. Indeed, interesting results have been reported involving biological membranes exposed to ELF-EMF [34,35].

Morelli et al. determined that ELF-EMF of 75 Hz with amplitudes reduces the enzymatic activities of three membrane-bound enzymes by 54–61% [36]. Falone et al. showed the main antioxidant and glutathione (GSH) dependent detoxifying enzymatic activities in control and ELF-EMF-treated neuroblastoma cells. Clearly, although ELF exposure significantly increased the activities of glutathione S-transferase and glutathione peroxidase (GSH-Px), it did not affect those of catalase, glutathione reductase, or SOD. Falone et al. tested the potential ELF-EMF-dependent modulation of cellular vulnerability in order to investigate the antioxidant effect of ELF-EMF exposure. They reported similarly induced mortality of hydrogen peroxide in cells exposed to ELF to that of the control group. In contrast, a significant increase in ROS production of neuroblastoma cells exposed to long-term ELF-EMF was observed following H2O2 incubation. However, antioxidant treatment with N-acetyl cysteine restored an increase in ROS levels back to normal [37].

Zwirska-Korczala et al. reported that exposing tissues to ELF-MF for 36 min a day had no effect on cell numbers after 24 h and 48 h of incubation. However, they showed a significant decrease in the activities of copper-zinc-containing SOD and manganese (CuZnSOD and MnSOD) isoenzymes and a significant increase in catalase activity after 24 h in the ELF-MF exposed group compared to the unexposed group and the control group. No significant difference was determined in the activities of glutathione reductase (GSSG-Rd) and glutathione peroxidase (GSH-Px) between the two groups. Surprisingly, after 48-h incubation, all enzyme activities HAD decreased, except for GSSG-Rd, in which no changes were noted. Exposure of ELF-MF to malondialdehyde (MDA) after 24-h incubation showed a significant increase in comparison to the control group. However, after 48 h of incubation, a significant decrease in MDA levels was seen in the control and ELF-MF exposed groups [38].

Tiwari et al. evaluated the potential biological effects of ELF-EMF on operatives working on power lines for electricity transmission networks and electric utility company workers in areas exposed to 132 kV high voltage areas in Hyderabad, India. They classified the workers into three groups based on their jobs; the administration group represented the lower exposure group, the maintenance operators the medium exposure group and the live line workers the higher risk group. All groups were matched with a control group in terms of age and socioeconomic status. EMF exposure exhibited a suppressor effect on plasma melatonin levels in the high exposure group. In addition, significant increases in the oxidant levels of nitric oxide (NO) and plasma MDA were reported for all exposed groups [39].

Further studies by Friedman et al. reported extracellular superoxide production through stimulation of plasma membrane NADH oxidase by RF-EMW. This stimulation leads to an increase in oxidative stress, and subsequently carcinogenesis. Rao et al. reported a significant increase in levels of intracellular Ca2+ against non-thermal RF-EMW and observed the effects of RF-EMW on the plasma membrane and calcium levels of stem cell-derived neuronal cells [40].

3.1. Alterations in plasma hormone levels following long-term exposure to EMF

Exposure to EMF induces ROS generation via different pathways in animal and human tissues [41,42]. EMF may injure the protective enzymatic and non-enzymatic antioxidant systems, and cell damage may occur as a result [43]. Levels of enzymatic and non-enzymatic antioxidants and oxygen consumption are higher in newborns compared to adults. GSH is an antioxidant found in mammalian cells, and GSH-Px is an antioxidant enzyme against oxidative damage caused by ROS [44]. One study of the uterus of rats exposed to 900-, 1800-, and 2450-MHz EMF showed that a decrease in the GSH-Px activity might cause an increase in lipid peroxidation. In contrast, there was no significant alteration in GSH levels in the uterus of growing rats. This may be due to the adaptive antioxidant responses of GSH accompanied by GSH-Px enzymatic activity up-regulation. TRPV1-mediated Ca2+ leads to accumulation of oxidative stress in the rat uterus. Mitochondrial dysfunction subsequently occurs by opening the mitochondrial membrane pores (Fig. 3) [45]. In another study, plasma luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels were observed to
Fig. 4. The role of glucose in brain functioning. Glucose metabolism regulates the vagal nerve and neuroendocrine signals and provides energy for neurotransmission. Histological images of the pancreas, duodenum, liver, and large intestine (Hematoxylin and eosin staining, scale bars: 100 μm and 200 μm). A: Pancreas tissue, B: Stomach tissue, C: Liver tissue, D: Large intestine. Glu: Glutamate, GluR: Glutamatergic receptors, Gln: Glutamin, EAAT: excitatory amino acid transporters, GLUT1: glucose transporter 1, (Modified from [58,59]).

decrease in rats exposed to 900-MHz EMF. Another study reported that serum progesterone, estrogen, and FSH levels decreased in female rats exposed to a 50-Hz sinusoidal magnetic field for 18 weeks [46,47]. Similarly, Woldanska-Okonska et al. demonstrated a decrease in blood progesterone, prolactin and estrogen levels in men resulting from exposure to 50Hz EMF [48]. Another experimental study observed no changes in serum prolactin levels in men following short-term exposure to 900-MHz EMF [49].

3.2. Overview of the effects of EMF exposure on glucose metabolism

Glucose is required for the synthesis of precursors for neurotransmitters and for the control of apoptotic pathways by glucose-metabolizing enzymes. Disruption in this pathway thus causes brain diseases. The blood to brain concentration facilitates the transport of glucose in the endothelial membranes by glucose transporter 1 (GLUT1) (Fig. 4). In particular, glucose is an essential source of energy and is necessary for both neurons and astrocytes. However, the blood glucose is most important to the brain, which acts as main sources of energy for brain tissue. The mechanisms of magnetic field effect on brain glucose metabolism are still not clear as in clinical studies [2]. High frequency (920-MHz) EMF exposure reduces brain glucose metabolism. In addition, while transcranial magnetic stimulation (TMS) at short intervals (<5 ms; >200 Hz) leads to neuronal inhibition, longer intervals (8–30 ms; 10–30 Hz) result in neuronal activation [50–53]. The mechanisms of the effects of magnetic field on brain glucose metabolism are still the subject
of debate. Elferchichi et al. have investigated the general effects of 128 mT static magnetic fields on glucose metabolism in the rats [54,55]. However, new studies about the effects of 900-MHz EMF on enzymatic reactions involved in glucose metabolism also are required. Although the effects of extremely low frequency EMF on enzymes in the glucose metabolism have been extensively demonstrated, experimental studies on the effects of GSM modulated EMF effects on glucose metabolism is limited [56]. Shi et al. have studied on Caenorhabditis elegans that was exposed to 50 Hz ELF-EMF at intensities of 0.5, 1, 2, and 3 mT by encoding the enzymes involved in glucose metabolism and reported an increase in the energy metabolism after exposure [56]. Harakawa et al. have studied on rats exposed to 50 Hz EMF and observed a significant increase in the plasma ACTH and glucose and plasma lactate levels. Low-dose EMF has been shown to cause a decrease in plasma lactate levels in rats with stress [57]. The metabolic pathways are not fully explained; although the stress caused by both low dose and high dose EMF exposure affect the energy metabolism.

4. Potential effects of EMF exposure on brain hormones

The effect of RF-EMF at different frequencies on human health is questioned by many studies. In this context, various strategies have been applied using in vivo and in-vitro methods in epidemiological and experimental studies. The effects of RF-EMF exposure are a common problem associated with mobile phone use in radiation studies. Behavioral and neurophysiological measurements are very important in evaluating the side effects of EMF exposure on the nervous system [60,61]. On the other hand, some behavioral studies have reported positive effects on learning after exposure to mobile phone radiation as to increase through radiation itself or by thermal to enhance the blood supply circulation and effects on electron arrangement [62–65]. These results have led to a new discussion of RF-EMF exposure and to a need for further studies on the subject.

Volkow et al. reported a significant increase in brain glucose metabolism in humans exposed to mobile phone radiation in their study using positron emission tomography [66]. Similarly, Kwon et al. investigated the effects of EMF on the brain. Both studies reported a suppressor effect of EMF emitted from mobile phones on brain glucose metabolism. However, they observed no effect of EMF exposure on the brain blood barrier. The clinical reflection of the effects of mobile phone radiation on brain glucose metabolism is still controversial and the EMF effect on the chemical stability of hormones of the brain, have some weak chemical bond due to the EMF effect gives different chemical bonds in strand chemical hormones [61].

Çelik et al. recently investigated the effects of antioxidant redox systems against EMF in the rat brain and liver during gestation and development. They reported decreased GSH-Px level activity, concentrations of vitamin A and vitamin E and increased lipid peroxidation levels in the brain and liver exposed to 2.45-GHz EMF. In addition, reduced levels of GSH and vitamin C were determined in the brain [67]. Some studies have reported that EMF impulses may cause a degree of sensitivity in certain individuals [68]. Several studies have shown that exposure to EMF leads to alterations in cognitive functions or physiological parameters [69–72]. Regel et al. have studied on the effects of a RF-EMF resulting from base station-like signal on the cognitive functions in the healthy subjects and observed no short-term effect of RF-EMF exposure [69]. Similarly, Kleinlogel et al. have investigated the effects of new Universal Mobile Telecommunications System (UMTS) technology on cognitive functions and the resting EEG. They studied on mobile phone user at different frequency, from 900 to 2000 MHz for over five weeks and reported that no effect was observed EMF emitted by mobile phones at from 900 to 2000 MHz on well being and resting EEG [70]. In consistent with these human studies, Unterlehener et al. have suggested that EMF emitted by UMTS signal had no effect on the attention [71]. In addition, Eltit et al. have studied on the effects of RF-EMF emissions of UMTS on human with idiopathic environmental illness and detected short-term exposure to base station-like signals did not affect the cognitive and physiological functions in the sensitive and healthy individuals [72]. One study reported an increase in headache ratings in the adolescents and adults following exposure to RF-EMF emitted by mobile phones. However, no change was observed in cognitive function and memory after RF-EMF exposure [73]. The adverse effects of EMF on human health can vary depending on the exposure duration rather than the frequency. In this context, epidemiological researches on long-term exposure are needed to clarify these effects. One study reported an increase in headache ratings in the adolescents and adults following exposure to RF-EMF emitted by mobile phones. However, no change was observed in cognitive function and memory after RF-EMF exposure [73]. The adverse effects of EMF on human health can vary depending on the exposure duration rather than the frequency. In this context, epidemiological researches on long-term exposure are needed to clarify these effects.

The synaptic efficacy of neural mechanisms in the brain and the role of EMF exposure on the central nervous system may be correlated with higher brain functions. One study investigated synaptic plasticity in the rat hippocampus and reported a decrease in synaptic activity in the hippocampal region of the brain after ex-vivo 50 Hz-EMF exposure [74].

5. Current knowledge of the impacts of EMF on circadian rhythms

Melatonin produced by the pineal gland is a natural hormone regulated by the suprachiasmatic nucleus. The balance between darkness and light controls the circadian rhythm. Beside of it, some researchers have also investigated the free-radical scavenger effect of melatonin. Melatonin accumulates in the central nervous system at high levels compared to those in blood since it crosses the blood-brain barrier and associated with the immune system [75–77]. Additionally, it is important in the control of many physiological processes, such as sleep and reproduction [78].

A relationship between melatonin levels and an increased incidence of breast cancer is controversial. This risk may result from reduced production of melatonin at night. In contrast, Davis et al. demonstrated no association between an increased risk of breast cancer and exposure to magnetic fields [79]. Naziroglu et al. and Kumar et al. have looked at the effects of 2450 MHz and 100 MHz EMF on male infertility and modulation and the production of melatonin. Kumar et al. have concluded that EMF has adverse effect on male fertility by means of reducing MDA and melatonin levels. In addition, Naziroglu et al. have suggested the neuroprotective effects of melatonin against EMF exposure by affecting calcium homeostasis. In contrast to human studies regarding short-term effects of EMF, they have found the deleterious effects of 2450 MHz EMF emitted by wireless on cognitive functions of rats [80,81]. Melatonin has been shown to exhibit a protective effect against ionizing radiation [82]. In addition, epidemiological studies have reported that the effects of magnetic fields on melatonin and its metabolite, 6-sulfoxy melatonin, in humans [83–86]. Burch et al. have investigated the effects of 60-Hz magnetic field on the melatonin levels of electrical utility workers [83]. Similarly, Burch et al. also have explained the biological mechanism of adverse effects of 60-Hz EMF on health by suppressing melatonin [84]. In consistent with other studies, Gobba et al. have measured 6-hydroxymelatonin sulfate excretions and reported that melatonin...
secretion can be affected by occupational exposure to EMF [85]. A decrease in the excretion of 6-sulfatoxy melatonin in urine in humans exposed to low frequency EMF has been reported. Melatonin has been shown to exhibit a protective effect against ionizing radiation [82]. In addition, epidemiological studies have reported that the effects of magnetic fields on melatonin and its metabolite, 6-sulfatoxy melatonin, in humans [83–86], Burch et al. investigated the effects of 60-Hz magnetic field on the melatonin levels of electrical utility workers [83]. Similarly, this group also explained the biological mechanism of adverse effects of 60-Hz EMF on health by suppressing melatonin [84]. In consistent with other studies, Cieby et al. have measured 6-hydroxymelatonin sulfate excretion and reported that melatonin secretion can be affected by occupational exposure to EMF [85]. A decrease in the excretion of 6-sulfatoxy melatonin in urine in humans exposed to low frequency EMF has been reported [83–87]. In addition, a 60-Hz magnetic field has been reported to reduce the activity of the pineal gland in women [28]. Similarly, the use of cellular phones for more than 25 min (daily) has been shown to reduce melatonin secretion [88]. In this context, according to Burch et al., the stability of EMF may play a key role in eliciting the adverse effects on human health by suppressing 6-hydroxymelatonin sulfate excretion. In addition, a 60-Hz magnetic field has been reported to reduce the activity of the pineal gland in women [28]. Similarly, the use of cellular phones for more than 25 min (daily) has been shown to reduce melatonin secretion [88]. In this context, according to Burch et al. (1998), the stability of EMF may play a key role in eliciting the adverse effects on human health by suppressing 6-hydroxymelatonin sulfate excretion [83].

6. Conclusion

During the past two decades, numerous scientific data have shed light on the effects of EMF exposure on biological systems and human health. The human body exposes to two types of EMF, as ELF or RF [86]. A variety of biological and medical endpoints have been addressed in these studies. Brain hormones such as melatonin and alteration or suppression of the mechanisms thereof are associated with physiological disturbances such as sleep disorders, depression, stress, and cancers. However, the effect of EMFs on enzyme activity, membrane-bound enzyme activity or on soluble isoforms of adenylate kinase and on the activities of soluble enzymes is reported to be negligible. On the other hand, the dose of EMF in experimental animal studies extend between (50 Hz or 900 MHz) and these doses in human body not exceeded more as in mobile phone or electric towers, and also the material mass which faces to exposure of EMF in addition to the duration of exposures. This indicates that the membranes may play substantial roles in mediating enzymatic activities. This review shows the biological and health effects of EMF exposure. However, it should be kept in mind that most results in this field are still controversial.

Furthermore, in the evaluation of the adverse effects of low and high dose EMF on energy metabolism and hormonal regulation, stability of EMF and exposure duration have a significant role. Underlying mechanisms may vary depending on magnetic intensity. In this context, experimental and epidemiological studies regarding the adverse effect of EMF exposure on hormonal and enzymatic activity as well as other systems is still required.

Conflict of interest

The authors confirm that no part of this work has been submitted or published elsewhere and that no conflicts of interest apply.

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