Melatonin: A Potential Shield against Electromagnetic Waves

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Abstract: Melatonin, a vital hormone synthesized by the pineal gland, has been implicated in various physiological functions and circadian rhythm regulation. Its role in the protection against the non-ionizing electromagnetic field (EMF), known to disrupt the body’s oxidative/anti-oxidative balance, has been called into question due to inconsistent results observed across studies. This review provides the current knowledge on the interwoven relationship between melatonin, EMF, and oxidative stress. Based on synthesized evidence, we present a model that best describes the mechanisms underlying the protective effects of melatonin against RF/ELF-EMF-induced oxidative stress. It has been observed that the free radical scavenger activity of melatonin can be enabled by reducing the radical pair singlet-triplet conversion rate and the concentration of the triplet products. Moreover, this review aims to highlight the potential therapeutic benefits of melatonin against the detrimental effects of EMF, in general, and electromagnetic hypersensitivity (EHS), in particular.

Keywords: Antioxidant system, electrohypersensitivity, electromagnetic field, melatonin, oxidative stress, radical pair mechanism.

1. INTRODUCTION

The pineal gland has baffled philosophers and scientists in the past. In his dualistic theory, the French philosopher Rene Descartes stated that the pineal gland was the seat of interaction between the soul and the mind, while others, in the 19th century, named it the “third eye” [1, 2]. The mysticism surrounding the pineal gland was unraveled by the advent of neuroimaging and the discovery of its function as a source of melatonin in 1958 [2]. The pineal gland is shaped like a pine cone and positioned in the posterior part of the cranial fossa between the two thalamic bodies [3]. It receives sympathetic afferent innervation from the superior cervical ganglion and parasympathetic innervation from the optic and pterygopalatine ganglia [3]. The light/dark cycle controls the secretion of melatonin by the pinealocytes in the pineal gland to establish the circadian rhythm [4]. Reiter referred to melatonin as “the chemical expression of darkness” since its level increases during the night [5]. Light, on the other hand, is visible electromagnetic radiation that inhibits the synthesis of melatonin [5]. This observation had led scientists to formulate a hypothesis connecting melatonin and electromagnetic field (EMF). Nevertheless, some would argue that the drop in melatonin levels is due to an increase in its utilization by the body against the oxidative stress induced by EMF [5]. The adverse health impact of EMF has created an urgency to study its mechanisms of action in the human body. This was deemed vital with the emergence of electromagnetic hypersensitivity (EHS) syndrome, in which affected individuals exhibit neuropsychiatric symptoms such as sleep disturbance and depression upon exposure to EMF [6]. Although EHS is not officially recognized by the World Health Organization (WHO) or the medical community as a medical disorder, there is a growing need to address it as a medical condition [7]. Studies using functional magnetic imaging (MRI) have revealed consistent brain abnormalities in patients suffering from EHS [8]. Exposure to EMF at 60Hz was associated with physiological disturbances such as headache, pain, and twitching [9]. Another study demonstrated that microwave exposure was associated with cardiac problems in addition to memory issues, fatigue, sleep disturbance, and dizziness, which were experienced by patients complaining of EHS [10]. Despite the scarcity of studies that examined the underlying pathophysiological mechanisms of EHS, the negative symptoms induced by repeated exposure to EMF were attributed to several factors, namely the bioaccumulation of electromagnetic toxicants that induce immune dysfunction, and catecholamine dysregulation that affects the autonomic nervous system. In addition, heavy metal deposition induced by EMF and its mobilization in tissues have also been identified as a potential cause of EHS [11]. However, and more importantly, it was the idea of excessive oxidative stress that gained ground as the main mechanism through which EHS occurs [12]. In this review, evidence for the connection between melatonin and EHS is presented, with a special focus on the role of melatonin as a protective agent against EMF-induced oxidative stress. The first part of the review discusses the metabolism of melatonin and its protective role against...
oxidative stress. We then provide an overview of the relationship between EMF, oxidative stress, and melatonin and discuss the potential therapeutic role of melatonin in reversing the effect of non-ionizing EMF, particularly in individuals suffering from EHS.

2. MELATONIN: ITS METABOLISM AND POTENT ANTIOXIDANT ROLE

Melatonin synthesis by pinealocytes is controlled by paraventricular nuclei (PVN) of the hypothalamus [4]. Neurons of the PVN project to the intermediolateral cell columns of the upper thoracic tract (T1/T3), where they synapse with preganglionic sympathetic cell neurons [4]. In the superior cervical ganglion, the preganglionic sympathetic neurons that innervate the cervical ganglion, the preganglionic neurons in turn synapse with preganglionic sympathetic cell neurons [4]. In the superior cervical ganglion, the preganglionic neurons in turn synapse with the postganglionic sympathetic neurons that innervate pinealocytes and secrete norepinephrine (NE) [4]. Norepinephrine (NE) binds to beta and alpha-adrenergic receptors triggering cAMP-PKA-CREB and PLC-Ca\(^{2+}\)-PKC downward cascades, respectively [4]. Binding of NE to beta-adrenergic receptors leads to increased intracellular cyclic 3',5'-adenosine monophosphate (cAMP) that activates protein kinase A (PKA) while binding to alpha-adrenergic receptors results in increased calcium ion (Ca\(^{2+}\)) concentrations and activation of protein kinase C (PKC) [4]. In rodents, PKA phosphorylates transcription factor cyclic AMP response element-binding protein (CREB), which increases the transcription of arylalkyl amine N-acetyl transferase (AANAT) [13]. AANAT is an enzyme involved in melatonin biosynthesis through which the regulation of melatonin occurs [13]. In primates, however, the mechanism differs in which PKA directly phosphorylates AANAT [13]. In both species, AANAT is protected through various mechanisms. This is done either by maintaining phosphorylated CREB (P-CREB), in rodents, or by posttranscriptional modification, in primates, which protects AANAT from degradation by proteasomes [13]. The drop in NE caused by light detection offsets the cascade pathways in pinealocytes controlling melatonin synthesis. In rodents, for example, light decreases NE secretion, causing dephosphorylation of P-CREB and reducing AANAT gene transcription [14].

The light/dark cycle affects the function of the pinealocytes in different ways, with the suprachiasmatic nuclei (SCN) acting as the transducer of photodendritic function [15]. Light hitting the retina depolarizes the ganglion cells that contain melanopsin and travels to the SCN through the retinohypothalamic pathway [16]. This direct retinal innervation allows the circadian rhythm of the body to be set according to the dark/light cycle perceived. However, it is beyond the SCN that the effect of melatonin is decoded as the SCN is similar in nocturnal and diurnal animals while melatonin has opposite outcomes in both types [17, 18].

Melatonin is synthesized through a series of hydroxylation, decarboxylation, acetylation, and methylation processes initiated with the uptake of L-Tryptophan from the bloodstream by pinealocytes [19]. Tryptophan hydroxylase converts tryptophan to 5-hydroxytryptophan, which is then decarboxylated by L-aromatic amino acid decarboxylase to serotonin (5HT) [19]. AANAT utilizes acetyl coenzyme A to acetylate serotonin into N-acetyl serotonin (NAS) [4]. Finally, N-acetyl serotonin O-methyl transferase (ASMT) converts N-acetyl serotonin into melatonin (N-acetyl-5-methoxytryptamine) [4]. The catabolism of melatonin mainly occurs through the action of cytochrome P\(_{450}\) isoenzymes that convert it to 6-hydroxymelatonin in the liver and brain as well [20]. This product is then sulfated by sulfotransferase and consequently excreted in the urine as 6-sulfatoxymelatonin, representing blood melatonin level [20]. Nevertheless, there are other pathways for melatonin catabolism, especially in the cases of external sources of stress (radiation) and inflammation [20, 21]. Under such conditions, melatonin is hydroxylated through interacting with hydroxyl radicals (•OH) into various products that act as powerful free radical scavengers [20, 21]. N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) is one product that can be upregulated by interferon \(\gamma\) upon inflammation [21].

Melatonin binds to membrane-bound G-protein coupled receptors MT1 and MT2, which, in humans, are represented by MTRN1A and MTRN1B, respectively [22]. MT1 and MT2 are found in various parts of the central nervous system (e.g., SCN, hippocampus, and thalamus) and in peripheral tissues (e.g., ovary, arteries, skin, and liver), with MT2 being mostly located in the brain [18]. Melatonin also binds to enzymes quinone reductase 2 or MT3 to limit oxidative stress [23]. Melatonin receptors are shown to affect multiple transduction pathways. For instance, the binding of melatonin to MT1 or MT2 receptors inhibits adenyl cyclase, leading to a decrease in cAMP and PKK, which further prevents the phosphorylation of CREB [24]. On the other hand, these melatonin-bound receptors activate phospholipase C (PLC), leading to a rise in protein kinase C (PKC) [24]. It is also worth noting that the binding of melatonin to MT2 receptors inhibits guanylyl cyclase and cyclic guanosine monophosphate (cGMP) levels [18, 25].

Melatonin acts as a hydroxyl scavenger and suppresses oxidative damage due to its chemical properties [26]. Since melatonin is an amphiphilic molecule, it is able to carry its protective function in a vast array of cellular parts, including lipid and aqueous compartments [27]. Melatonin and its derivatives possess a ring rich in electrons, making them ideal electron donors to neutralize free radicals [27]. Thus, unlike most free radical scavengers, which neutralize one molecule at a time, melatonin and its many metabolites, such as N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK), can detoxify multiple oxidizing molecules. Another mechanism is the ability of melatonin to bind heavy metals, which may contribute to oxidative damage leading to neurodegenerative diseases [28]. High levels of copper in the brain generate free radicals damaging to neural tissue, as evident in patients with Alzheimer’s disease (AD) and Parkinson’s disease [29]. Melatonin and its metabolite AFMK can intercalate the copper metal, preventing its detrimental effect, in high concentrations, on the brain [29]. Furthermore, melatonin protects from oxidative stress not only by acting as a free radical scavenger but also indirectly through activating potent antioxidants, like glutathione peroxidase, superoxide dismutase, and catalase [30].

From an evolutionary perspective, it is interesting to note the connection between melatonin and mitochondria [19, 31, 32]. Mitochondria contain the highest concentration of melatonin compared to other organelles [32]. It houses a series of
redox reactions necessary to generate adenosine triphosphate (ATP), making it rich in free radicals [32]. Melatonin is shown to be actively transported across the cellular membrane through human peptide transporters PEPT1/2 [32, 33]. Once inside the cell, it targets the mitochondria, thereby reducing oxidative stress and aging [32]. A delay in aging prevents the development of age-related diseases, such as cardiovascular disease, cancer, fibrosis, and multiple sclerosis, among others [32]. In clinical settings, melatonin proved to be effective for the treatment of several conditions. For instance, Chang and colleagues showed that melatonin can protect human retinal cells from age-related macular degeneration by preventing apoptosis due to oxidative stress [34].

3. ELECTROMAGNETIC FIELD – THE BASICS

The advent of electromagnetic waves technology has many benefits in our daily lives. While it has many advantages, it is indubitably a major invisible pollutant of our natural environment. As Dr. Robert O. Becker said, “The greatest polluting element in the earth's environment is the proliferation of electromagnetic fields” [6]. The EMF spectrum can be divided into three groups: static field (0Hz), extremely low frequency (ELF) field (3Hz-3000Hz), and radiofrequency (RF) field (3000Hz-300GHz) [6]. According to the WHO, electric fields are generated from electric charges or voltage differences, while magnetic fields are created around moving electric charges and magnets [35]. Both fields are vector quantities with a direction and magnitude [35]. The SI units are volts per meter (V/m) for the electric field. The magnetic flux density (flux density or Tesla) for the magnetic field [35]. Hence, an electric field does not require a flowing current to be generated, which makes a plugged appliance an emitter of an electric field even when turned off. Electric devices are the main causes of low frequency electric and magnetic fields in our environment [35]. Other sources include TV and radio stations that emit high-frequency RF waves [35]. It is worth noting that most human sources of electromagnetic waves have a low frequency/long-wavelength characteristic, which leads to nonionizing radiation with less energy to break molecular bonds [35]. Although magnetic fields induce currents in the human body, ELF-EMF and RF-EMF do not typically impose adverse health effects but can result in many biological effects [35], and chief among them is the generation of free radicals and oxidative stress, a common denominator of many diseases. Static, ELF, and RF cause alterations in free radicals and oxidative stress molecules, leading to biological changes such as DNA damage, increased immune response, and disruption of neural transmission [36, 37].

The mechanism by which static and ELF-EMF impact free radicals is largely unknown; however, it has been suggested that electroreception mediated by radical pair production inside cytochromes could explain this impact from an evolutionary perspective [36]. Most notably, the radical pair mechanism elucidates how RF/ELF-EMF can impact the rate and yield of chemical reactions involving radical pairs [38]. A radical is an atom or a group of atoms that has an odd number of electrons resulting in an unpaired electron spin. In one of two states, the spin can be found up (spins clockwise on its axis) and down (spins counterclockwise on its axis). A radical pair, on the other hand, is a brief reaction intermedi-ate generated when two radical species engage with each other in solution. Electron transfer leads to the formation of radical pairs that interact by an internal magnetic field due to the spin of the radical pair electrons [39]. The two unpaired electrons, one in each radical molecule, can have either an opposite spin (σ→), a singlet state, S) or the same spin (↑↑, a triplet state, T). The transition and chemical fates of these S and T states are impacted by several factors, particularly external and internal magnetic fields [39]. According to Hund’s rules, bonds can only form between electrons of opposite spin, suggesting that singlet state radical pairs can reform a bond, but those in triplet state do not do so and only proceed to form products [39]. The application of an EMF favors this formation of triplet products through Zeeman interactions between the radical pair electron spin and an external magnetic field [39]. Hence, we suggest that RF/ELF-EMF accentuates the singlet-triplet conversion in radical pair reactions, leading to an increase in triplet radical pair concentrations that eventually increase oxidative stress. For example, a weak RF magnetic field affects the formation of reactive oxygen species (ROSs) from hydrogen peroxide (H₂O₂) and superoxide (O₂⁻) [40].

3.1. EMF as an Inducer of Oxidative Stress

EMF results in thermal and non-thermal physiological changes in the body [41]. Thermal effects are characterized by an increase in the temperature of the organ affected by radiation, while the non-thermal effects involve the generation of ROSs [41]. These are free radicals that can steal electrons from lipids in the cell membrane through a process called lipid peroxidation, resulting in additional free and fatty acid radicals and disruption of cellular function, especially in the mitochondria where membrane damage further reinforces lipid peroxidation [42]. Under normal conditions, ROSs are constantly synthesized but are contained by antioxidants that terminate lipid peroxidation [42]. The body’s antioxidant system is comprised of glutathione peroxidase (GSH-Px), catalase (CAT), superoxide dismutase (SOD), heme oxygenase (HO1), and most importantly, melatonin [41, 43]. Under certain conditions of ELF/RF-EMF exposure, this body’s oxidative/antioxidant balance is disrupted, as corroborated by many preclinical and clinical studies (Table 1).

3.1.1. RF-EMF and Oxidative Stress

A study found that people residing near mobile towers, which emit RF-EMF, exhibited a greater lipid peroxidation level compared to a control group in addition to polymorphisms in the genes coding for manganese superoxide dismutase (MnSOD) and CAT [44]. More specifically, genotypic analysis of residents exposed to RF-EMF showed single nucleotide polymorphisms (SNPs) consisting of a CAT C262T polymorphism and a MnSOD Val9Ala polymorphism associated with increased lipid peroxidation [44]. Furthermore, high levels of lipid peroxide were detected in plasma samples of volunteers subjected to 900MHz RF-EMF from phones [45]. In their erythrocytes, there was a significant decrease in the activities of SOD and GSH-Px but not in CAT [45]. On the other hand, in a study conducted by Kerimoglu and colleagues, rats exposed to EMF at 900MHz in adolescence had increased SOD and CAT activities [46]. Also, there was an increase in malondialdehyde (MDA),
Table 1. Human and animal studies investigating the effect of EMF on oxidative stress.

| EMF Type                              | Experimental Group/Model                      | Main Findings                                                                 | References |
|---------------------------------------|------------------------------------------------|-------------------------------------------------------------------------------|------------|
| **Human Studies**                     |                                                |                                                                               |            |
| RF from mobile towers                 | 116 residents near mobile towers and 106 residents at least 800m away | Polymorphisms in antioxidant MnSOD and CAT genes leading to their low activity and high lipid peroxidation | [44]       |
| RF 900MHz from phone                  | 12 male volunteers                             | Increase in plasma lipid peroxide and decrease in SOD and GSH-Px activity in human erythrocytes; No significant decrease in CAT | [45]       |
| ELF-EMFs of 110-420 kV power lines with or without GTPS | 867 workers                                    | Increased urinary 8-isoprostane and 8-OHdG reduced after 12 months of GTPS | [50]       |
| **Animal Studies**                    |                                                |                                                                               |            |
| RF at 1950 MHz for 8 months           | 24 (14-month-old) and 5 (3-month-old) C57BL/6f female mice | No long term effect for RF-EMF on age-induced oxidative stress or neuroinflammation | [47]       |
| RF-EMF at 900 MHz for 1 h in adolescence | 24 male Sprague Dawley rats, aged 21-59 days              | Oxidative damage by increasing MDA, SOD, and CAT levels; Thickening of the epineurium of the sciatic nerve | [46]       |
| RF at 900 MHz                         | 20 Samaritan rat models of AD                 | Increased hippocampal HO1 staining and oxidative stress and reduced corticosterone levels | [49]       |
| ELF-EMF at 50 Hz, magnetic field 0.1mT for 10 days | 20 (3-month-old) and 20 (19-month-old) female Sprague Dawley rats | Increased antioxidant activity (MnSOD,CAT, &GSH-Px) in young but not aged rats | [55]       |
| ELF-EMF at 50 Hz, 0.97 mT              | 48 female Wistar rats                          | Oxidative DNA damage and lipid peroxidation and increase in 8-OHdG and TBARS levels | [51]       |
| ELF-EMF at 50 Hz for 28 days with 22 hours per day | 20 male Wistar rats                           | No effect on oxidative stress in specified brain parts | [53]       |

**Abbreviations:** 8-hydroxy-2-deoxy-guanosine (8-OHdG); catalase (CAT); glutathione peroxidase (GSH-Px); green tea polyphenol supplementation (GTPS); heme oxygenase (HO1); malondialdehyde (MDA); manganese superoxide dismutase (MnSOD); 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX); superoxide dismutase (SOD); thiobarbituric acid reactive substances (TBARS).

which is a byproduct of lipid peroxidation indicative of oxidative damage [46]. In addition, this study investigated the effect of phone EMF on the sciatic nerve and noted an increase in the thickness of the epineurium of this nerve [46]. Taken together, the above findings may indicate that EMF does not affect the activity of antioxidant enzymes uniformly but disturbs their normal balance, possibly through various interactions and parameters. In middle-aged and young rats, long-term RF-EMF exposure at 1950MHz did not show any effect on age-related oxidative stress and DNA damage [47]. In this study, the biomarkers used for oxidative stress were 3-nitro-tyrosine (3-NT) and 4-hydroxy-2-nonenal (4-HNE), indicating protein nitration and lipid peroxidation, respectively [47]. Nonetheless, it would have been of value to check the levels of antioxidant enzymes to determine whether their increase suppresses RF-EMF-induced lipid peroxidation.

The effect of electromagnetic field on free radicals and oxidative stress associated with AD has also been investigated in humans and rats, although the outcome measurements were inconsistent. In one of the studies, it was observed that exposure to RF at 918MHz protected human and rat astrocytes from oxidative stress induced by amyloid-beta (Aβ) and H2O2 [48]; while in another, RF at 900 MHz was shown to induce oxidative stress and increase the activity of hippocampal OH-1 in AD rat models [49]. The contrasting findings could be attributed to differences in models and exposure parameters. Due to the paucity of research in this field, more work is needed to understand the effect of RF radiation on oxidative stress generated due to AD.

### 3.1.2. ELF-EMF and Oxidative Stress

When hydroxyl radicals attack DNA strands, byproducts, such as 8-hydroxy-2-deoxy-guanosine (8-OHdG), are obtained. Thus, 8-OHdG serves as a biomarker for DNA damage, oxidative stress, and cancer [43]. Zhang et al. found an increase in urinary 8-OHdG following ELF-EMF exposure [50]. This was decreased after 12 months of green tea polyphenol supplementation but not maintained beyond that [50]. Similarly, 50 Hz of ELF-EMF induced oxidative damage and lipid peroxidation in male rats with increased 8-OHdG [51]. Moreover, ELF-EMF was found to affect the male reproductive system and possibly induce male infertility by decreasing normal sperm count. It has been observed that EMF caused apoptosis in mouse spermatogonia through oxidative stress, DNA damage, and consequent p53/21- cell cycle
Table 2.  Human and animal studies investigating the effect of EMF on melatonin levels.

| Experimental Conditions | Experimental Model/Group | Main Findings | References |
|-------------------------|--------------------------|---------------|------------|
| **Human Studies**       |                          |               |            |
| RF-EMF at 8-12GHz and 12.5-18GHz exposure up to 10 years or more | 155 male military men | A minor decrease in plasma melatonin at 8-12GHz EMF | [76] |
| RF-EMF 6–22 MHz from a radio transmitter | 54 people residing near the transmitter | Reduced salivary melatonin level by 10% during EMF | [75] |
| ELF-EMF: Geomagnetic activity and MF at 60Hz or ambient light | 153 male electric workers | Decrease in urinary 6-hydroxymelatonin sulfate | [68] |
| ELF-EMF: magnetic field at 60Hz for 5 consecutive nights | 115 women between 20 and 45 years old | Decrease in urinary 6-sulfatoxymelatonin | [69] |
| ELF-EMF at ≤0.2 µT and >0.2 µT | 59 workers | No effect on urinary 6-sulfatoxymelatonin with or without EMF | [66] |
| ELF-EMF: magnetic field at 50Hz | 10 men aged 20–37 | No effect on serum melatonin level | [65] |
| ELF-EMF: Magnetic field at 60Hz | 242 people aged 50-81 years | No effect on 6-sulfoxymelatonin level | [67] |
| ELF-EMF: 60-Hz magnetic field from the phone during 5 days or 13 days for >25 minutes per day | 77 male electric workers used phones for 13 days, and 149 used for 5 days (aged 18-60) | Decrease in urinary 6-hydroxymelatonin sulfate following 13 days of exposure | [70] |
| **Animal Studies**       |                          |               |            |
| RF-EMF: 1439 MHz time division multiple access (TDMA) EMF | 104 male and 104 female Sprague Dawley rats | No effect on pineal and serum melatonin level | [74] |
| RF-EMF at 383, 900, and 1800 MHz | 240 Djungarian hamsters | No effect on serum and pineal melatonin level Increase in body weight | [72] |
| RF-EMF at 900 MHz and 1800 MHz from phones for 30 days (30 min/day) | 30 male Sprague Dawley rats | No effect on serum melatonin level | [73] |
| ELF-EMF: magnetic field at 60Hz and 1000 mG for 1 month | 18 male Sprague-Dawley rats | Increase in urinary 6-sulphatoxymelatonin level | [60] |
| ELF-EMF at 12 and 1 Hz for 30 days at 4 hours /day (0.7µT) | 4 male rhesus macaques | Increase in plasma melatonin level | [57] |
| ELF-EMF: magnetic field at 50Hz from power lines | Wild kestrels in 28 MF exposed nests and 16 control nests | No effect on serum melatonin level | [58] |
| ELF-EMF: 50 Hz MF at 100 µT for 52 days | 60 female CD3F mice | No effect on nocturnal urinary 6-hydroxy melatonin sulfate level | [59] |

arrest [52]. The oxidative stress imbalance was correlated with the increasing frequencies at 2, 5, and 120Hz [52]. In another study, ELF-EMF at 50Hz failed to cause oxidative stress in multiple brain structures of rats, yet the activity of some antioxidant enzymes did increase in certain brain areas [53]. Finally, since aging is accompanied by exacerbated DNA oxidative damage [54], the impact of ELF-EMF on aged animals compared to young ones has been investigated. Exposure to a 50Hz magnetic field resulted in enhanced activity of antioxidant enzymes (CAT, SOD, and GSH-Px) in young rats but not in aged rats, showing a significant drop in CAT and glutathione-related antioxidant activities [55]. Hence, age presented a risk factor for ELF-EMF-facilitated oxidative stress in the nervous system [55].

In order to explain the variable impact of applying a magnetic field at different frequencies, we can suggest the following. First, in human studies, it is not completely possi-
Melatonin and its metabolites (Table 3.2. Effect of EMF on Melatonin Production
Preclinical and clinical studies were conducted to examine the effect of ELF/RF-EMF exposure on the levels of melatonin and its metabolites (Table 2). However, these studies have been conflicting, with several demonstrating suppression of melatonin production, while others showing no effect and some actually reporting increases.

3.2.1. ELF-EMF and Melatonin
In preclinical studies, the majority of the animals studied were nocturnal, including rats, mice, and hamsters. The exception was an experiment conducted on rhesus macaques, which were subjected to ELF-EMF at 1 and 12 Hz for 30 days [57]. In this study, blood samples of rhesus macaques displayed an increase in plasma melatonin levels [57]. In contrast, a study on wild kestrel chicks showed that a 50Hz magnetic field had no effect on the serum level of melatonin [58]. A similar result was also observed in mice subjected to a 50Hz magnetic field where urinary 6-hydroxy melatonin sulfate was sampled [59]. Interestingly, however, an increase in urinary 6-hydroxy melatonin sulfate was obtained upon ELF-EMF exposure at 60Hz in rats [60]. The discrepancies observed in the effect of ELF-EMF on melatonin synthesis could be attributed to the difference in radiation exposure level and its ability to alter the reaction rate of radical formation and the catalytic behavior of the chemical reaction [61].

As opposed to studies in humans, animal studies offer the advantage of measuring pineal melatonin levels. ELF-EMF at a frequency of 50 Hz failed to alter melatonin levels when directed at the pineal glands of Wistar rats [62], while a decrease in melatonin level was observed following the exposure of the pineal glands of Djungarian hamsters to EMF at a frequency of 16/50 Hz [63].

Several clinical studies have also investigated the effect of ELF-EMF at 50Hz exposure on melatonin levels in workers, with results showing no clear association between the two [64, 65]. For instance, the level of 6-hydroxy melatonin sulfate in workers failed to change after exposure to ELF-EMF over 3 complete workdays [66]. Similar to experiments on EMF and oxidative stress, age could be a factor in EMF and melatonin interactions. In a study conducted by Youngstedt and colleagues, ELF-EMF exposure at a frequency of 60 Hz failed to alter melatonin excretion in adults aged between 50-81 years [67]. It was hypothesized, however, that other factors, besides age, like weight, alcohol consumption, and medications, could interfere with the effect of EMF on melatonin levels [67]. Interestingly, in several human studies, EMF was shown to decrease melatonin levels. For instance, in a population of 153 male electric workers, geomagnetic activity combined with a 60Hz magnetic field led to a significant drop in urinary 6-hydroxymelatonin sulfate [68]. A significant decrease in urinary 6-sulfatoxymelatonin was also observed in a population of women aged between 20 and 45 years exposed to a 60Hz magnetic field for 5 consecutive nights [69]. Moreover, it was found that workers who used their phones (ELF-EMF at 60Hz) for more than 25 minutes per day for 13 days displayed a significant drop in urinary 6-hydroxymelatonin sulfate while the group who used it for only 5 days revealed no reduction [70].

3.2.2. RF-EMF and Melatonin
In the pineal glands of Djungarian hamsters, an increase in melatonin level was observed following exposure to RF-EMF at a frequency of 1800MHz [71]. Hamsters exposed to RF-EMF at 383, 900, and 1800 MHz exhibited an increase in body weight, but no effect on serum or pineal melatonin levels was noted [72]. However, RF-EMF at 900 MHz and 1800 MHz emitted from phones and directed at rats did not change serum melatonin level since, at the frequency used, the skin could shield the pineal gland from the EMF [73]. Moreover, short-term exposure to 1439 MHz RF-EMF did not alter serum or pineal melatonin levels [74].

The failure to show an impact of EMF exposure on human melatonin levels has deterred scientists from further investigating the connection between EMF and melatonin, as indicated by the significant drop in the number of studies during the last two decades. However, multiple observations can be noted in experiments that used RF-EMF. In Switzerland, a coincidental shutdown of a radio transmitter allowed scientists to compare the levels of melatonin in residents before and after shutdown. Results showed that exposure to the transmitter waves (6-22 MHz) suppressed salivary melatonin levels by 10%, yet after shutdown, melatonin levels rose by 15% [75]. Sleep quality, as reported by subjects, was also enhanced upon shutdown [75]. Interestingly, only people who had a bad quality sleep showed an association between EMF exposure and melatonin levels, suggesting that some individuals might be more susceptible to the effects of EMF depending on their sleep habits [75]. Also, another study showed that RF-EMF, at a frequency of 12.5-18 GHz, caused greater suppression of urinary 6-hydroxymelatonin sulfate than RF-EMF at a frequency of 8-12GHz, highlighting the importance of a higher frequency for a greater impact [76].

Collectively, the results of RF/ELF EMF studies further corroborate that an effect on melatonin by ELF/RF-EMF in humans differs with the duration of exposure and frequency used. From what has been presented, it can be inferred that EMF exposure disrupts normal physiological functions, which warrant compensatory mechanisms to reinstate balance. Melatonin could be one of the molecules disrupted by this stressor, but further studies are needed to reproduce the results obtained and compare the effect of changing specific parameters within the same experimental design. However, the inconsistencies in the reported findings indicate that this disruption could be due to an increase in melatonin utility as compensation for a lost balance rather than a direct impact of EMF on melatonin secretion [77]. It is possible that increased oxidative stress caused by shifting the reaction rate...
Fig. (1). The effect of RF/ELF-EMF on the singlet-to-triplet conversion of radical pairs that result in increased oxidative stress and subsequent activation of melatonin to exert a negative feedback control. **Abbreviations:** internal magnetic field ($B_{\text{in}}$); external magnetic field ($B_{\text{ex}}$); radiofrequency electromagnetic field (RF-EMF); extremely low frequency electromagnetic field (ELF-EMF).

of the radical pair mechanism towards the formation of triplet products signals negative feedback by activating melatonin. In turn, melatonin attenuates triplet products and decreases free radical concentrations by activating antioxidants or acting as a free radical scavenger. Furthermore, it has been suggested that varying the frequency in the RF or the ELF-EMF range can change the Zeeman states of the electrons and consequently the radical concentrations leading to biological changes [56]. This supports the suggested model that relies on radical pair mechanisms and spin states to explain EMF impact. However, it was shown that melatonin and its metabolites impact radical formation differently [78]. This could explain the importance of accounting for the effect of melatonin metabolites and precursors when studying the impact of EMF on oxidative stress and its reliance on melatonin for feedback control.

4. MELATONIN AS A RADIO-PROTECTIVE AGENT AGAINST EMF: IMPLICATIONS IN EHS

The decline in the number of studies investigating the effect of EMF on melatonin has been counterbalanced by a rise in studies investigating the antioxidant effect of melatonin on EMF-induced oxidative stress. The possibility that melatonin can act as a radio-protective molecule has gained interest in the scientific community. Weak magnetic fields can impact the concentration of radical pairs and lead to biological changes [79]. This is achieved by altering the radical pair electron spin state at different frequencies leading to singlet-triplet conversions that impact the reaction rate [56]. The resultant imbalance in oxidative/anti-oxidative systems signals a feedback process to compensate for increased ROS and free radicals [79]. Electron spin resonance (ESR) spin trapping experiments have shown that melatonin is capable of decreasing riboflavin-induced radical pair formation either by suppressing the triplet state of sensitizers or repairing the free radicals [80]. Thus, we suggest that melatonin’s antioxidant properties make it a potent molecule on which our body physiology relies to suppress EMF-induced oxidative stress by the aforementioned negative feedback control on radical triplet pairs (Fig. 1). Following this reinterpretation of the melatonin-EMF connection, studies on the protective role of melatonin against nonionizing EMF will be presented to suggest using melatonin in therapy for EHS.

Many studies have demonstrated the protective role of melatonin against non-ionizing radiations (Table 3). Investigators have looked at the possibility of using the antioxidant property of melatonin in order to fight EMF-induced oxidative stress in different tissues. In a study on 2450 MHz RF-EMF irradiated rats, melatonin was shown to reduce lipid peroxide and MDA/nitric oxide levels in erythrocytes and heart tissues, respectively [81]. In addition, levels of vitamin C and E were increased in melatonin-treated rats compared to control ones, indicating that melatonin enhances the antioxidant system [81]. EMF was also shown to increase oxidative stress in the eye. Lenses of rats exhibited a slight increase in lipid peroxidation levels upon exposure to RF-EMF at 2.45 GHz from wireless internet for 1 hour [82]. However, melatonin supplementation was able to increase GSH-Px in radiated rats to fight the resultant oxidative stress [82]. This finding is in agreement with another study on the retinas of rats, whereby melatonin increased the levels of the antioxidant enzymes SOD, CAT, and especially GSH-Px upon exposure to 900 MHz RF-EMF [83]. Furthermore, melatonin resulted in a drop in the levels of MDA and nitric oxide in the aforementioned retinas [83]. Melatonin supplementation was able to protect rat testicular cells from oxidative damage caused by RF-EMF at 2.45GHz through decreasing lipid peroxidation and increasing the levels of GSH-Px, vitamin E, and glutathione [84]. Similarly, it decreased MDA levels and increased GSH-Px to counteract the effects caused by
RF-EMF-induced oxidative stress at 900MHz in mice [85]. Hence, it was found that testis damage due to RF-EMF was reversed, and testosterone levels increased [85]. In the brain tissue of rats, melatonin was able to prevent oxidative damage but failed to prevent the decrease in CAT levels caused by microwave radiation from phones [86]. Also, both 2.45 GHz RF-EMF-induced lipid peroxidation and ROS levels were decreased in the brain of rats after melatonin administration [87]. Melatonin was able to prevent rat hippocampal cell loss caused by exposure to RF-EMF at 900MHz permanently [88]. In this study, the number of pyramidal cells in the cornu ammonis (CA) decreased significantly upon exposure to RF-EMF [88]. To investigate the mechanism by which melatonin protects cells from the effect of RF-EMF, electroencephalography spikes, calcium ion influx, and lipid peroxidation levels were recorded in rat brain and dorsal root ganglion irradiated with RF-EMF at 2.45GHz [89]. The results revealed that melatonin administration decreases lipid peroxidation, calcium ion influx, and electroencephalography spikes, indicating that melatonin possibly protects neuronal cells from EMF through voltage-gated calcium channels and transient receptor potential melastatin 2 (TRPM2) channels [89]. The influx of calcium ions across TRPM2 channels is the process by which H2O2 leads to necrosis [90]. This indicates that the gate is affected by changes in oxidative stress. Furthermore, melatonin resulted in an increase in the levels of vitamin E in the brain cortex but not in the levels of other antioxidants such as glutathione, GSH-Px, vitamin A, vitamin C, and beta carotene [89]. Overall, these studies in experimental animals suggested that melatonin provides radioprotective effects against RF/ELF EMF-induced oxidative stress; however, whether this effect extends to humans as well is yet to be investigated. Also, most of the animal studies have investigated melatonin’s effect against RF and not ELF-EMF, so studies investigating the radioprotective role of melatonin against ELF-EMF are warranted. The study investigating the exposure to 50 Hz ELF-EMF found that melatonin protected lymphocytes, extracted from male Albinor Wistar rats, from the induced DNA damage [91]. At a concentration of 0.5mM, melatonin caused a 50% decrease in the percentage of DNA-damaged lymphocytes, while a concentration of 1mM resulted in a 100% drop in damaged rat lymphocytes [91].

EHS can be the result of multiple EMF exposures or a single severe exposure [92]. It occurs over three main levels [12]. In the first level, temporary symptoms come and go, but in the second level, the severity and occurrence rate of the symptoms amplify. In the final level, patient with EHS experiences neurological disturbances caused by exposure to even minute degrees of EMF [12]. It is accompanied by many health effects such as insomnia, headache, irritability, dizziness, cognitive decline, and memory problems [12]. These health effects stem from physiological disturbances, which include inflammation, excess oxidative stress, changes in brain blood flow, and changes in brain glucose metabolism [12]. Excessive oxidative stress is proposed as the main mechanism through which EHS occurs [12]. It is suggested that an environmental stressor such as non-ionizing EMF creates a local mild inflammatory response that leads to histamine release by cells in the brain [7]. Histamine, in turn, induces oxidative stress in the brain, which, upon second exposure to the EMF stressor, disturbs the blood-brain barri-
er (BBB) and creates an augmented inflammatory response responsible for the symptoms observed [7]. Indeed, increased oxidative stress has been documented in people with self-reported EHS. Approximately 30-50% of self-reported EHS patients have increased oxidation and lipid peroxidation biomarkers, 60% have increased levels of SOD, while 19% have increased GSH-Px levels [93]. On the other hand, 20-40% had low glutathione-associated markers [93]. Interestingly, in human serum, the high levels of melatonin were significantly associated with a higher total anti-oxidant capability [94]. In a large-scale study, it was shown that self-reported EHS patients had low levels of urinary 6-hydroxy melatonin sulfate, suggesting the metabolite’s possible use as a biomarker for EHS [95].

The criteria to diagnose a patient with EHS are as follows. First, the patient should not have any disease that could be responsible for the observed symptoms [7]. Second, the patient presents the symptoms mentioned above with an emphasis on headache, tinnitus, and other neurological disturbances [7]. Third, the symptoms are triggered every time the patient is exposed to EMF and disappear in the absence of EMF exposure [7]. Finally, the patient presents Multiple Chemical Sensitivity (MCS), which is clearly diagnostically defined and is accompanied by EHS in most cases [7]. Patients with EHS are often prescribed vitamin supplements, as they possess vitamin deficiencies, antioxidants like glutathione, and antihistamine [7]. We have observed previously that melatonin has proven to be efficient in increasing the levels of specific vitamins (A, E and C) in the blood and fighting off increased oxidative stress indirectly by activating the body’s antioxidant system. Moreover, melatonin plays a major role not only as an antioxidant but also as an anti-inflammatory agent. For example, in a rat model of chronic inflammation, it was shown that as the concentration of administered melatonin increased up to 5mg/kg, the percentage of inflammation inhibition increased by suppressing the pro-inflammatory enzyme cyclooxygenase-2 (COX-2) [96]. In addition to melatonin, its metabolites N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) and N1-acetyl-5-methoxykynuramine (AMK) also exhibited an anti-inflammatory effect in macrophages by suppressing COX-2 and the inducible form of nitric oxide synthase (iNOS) [97]. These results are important because COX-2, which is essential for prostaglandin synthesis, and iNOS are both promoters of inflammation [97]. Thus, the effects of melatonin are aligned with the treatment procedures followed for an EHS diagnosis. If no treatment is administered to patients with possible EHS, then it is stated the disease may progress into more serious neurodegenerative and psychiatric disorders [7]. Interestingly, the functional and therapeutic role of melatonin is evident in several psychiatric disorders such as major depressive disorder, schizophrenia, and autism spectrum disorder [98]. Low levels of nocturnal melatonin were found in the serum of people diagnosed with the major depressive disorder compared to healthy ones [99]. Melatonin administration was found to downregulate depression and anxiety-related proteins and behavior in triple transgenic mice of AD, suggesting that melatonin may provide antidepressant effects [100]. In patients with schizophrenia, low melatonin release contributes to insomnia; thereby, the administration of 2mg of melatonin was able to enhance sleep quality [101]. Also, melatonin has proved to be efficacious in treating sleep troubles in children with autism [102]. Melatonin’s potent anti-oxidative properties and past clinical efficacy suggest that it can be helpful in ameliorating the symptoms of EHS patients. However, further studies in humans are needed to investigate the ability of melatonin to counteract EMF-induced oxidative stress and ameliorate the symptoms of EHS.

CONCLUSION

The various functions carried out by melatonin as an antioxidant and possible therapeutic drug prove that it is far more than just a sleep hormone synthesized by the pineal gland. Studies have also highlighted its ability to fight oxidative stress as a free radical scavenger or through activating antioxidant enzymes. Non-ionizing EMF, although safe, induces biological changes in the body by creating a state of excessive oxidative stress and enhancing lipid peroxidation. Using different approaches and techniques, the vast majority of studies on the effect of EMF on melatonin yielded contradictory and negative results in humans. However, the possibility that EMF affects the body’s utility of melatonin against an external stressor has shifted research towards investigating melatonin’s radio-protective role. In this review, we propose a model in which RF/ELF-EMF favors singlet-triplet conversion and leads to an increase in radical pairs in the triplet state that cannot form bonds. This creates an oxidant/anti-oxidant imbalance that necessitates feedback control through melatonin release. The suggested paradigm helps understand the discrepancies in the results obtained in the studies by showing that EMF parameters such as frequency and duration affect the electron spin states and radical pair concentrations. Although the focus has been directed at studying ionizing radiations, animal studies have presented the efficacy of melatonin against non-ionizing radiation, although mostly being RF studies. Thus, future studies investigating melatonin’s radio-protective role against non-ionizing radiations are warranted, considering their impact on the body’s oxidant-antioxidant balance. Nevertheless, our suggested mechanism is limited by the lack of specificity regarding the exact ROS that melatonin acts on to decrease oxidative stress in the most potent way. Future studies can benefit from carrying out spin trapping mechanisms on different free radicals to determine the specific reaction carried out by melatonin in the context of radical pair mechanism and Zeeman interactions to fight increased oxidative stress.

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CONFLICT OF INTEREST

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Melatonin, EMF and Oxidative Stress

Current Neuropharmacology, 2022, Vol. 20, No. 3

659

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