



Melatonin production influenced by low frequency magnetic fields

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Abstract

In several residential and occupational studies, suppression of nocturnal melatonin in humans, which is induced by magnetic field, has been reported. The pineal gland produces melatonin and consider it as its major secretory product, which has a vital role in human well-being and health as it was suggested by the growing literature. Generally, exposure to the electric field has many biological effects, and the research on which has recently made this neurohormone, which is associated with the generation and classification of electric field, a focal point. To raise the risk of cancer through changing the pineal glands' regular functions and disrupting the melatonin's nocturnal increase in its release and synthesis, exposure to magnetic fields has been hypothesized. It is very essential to ascertain whether hormonal levers are changed during the exposure of humans to a magnetic field at night because the evidence for the "melatonin hypothesis" relies chiefly upon rodent data. The field-induced alterations were failed to be observed by all studies which have investigated the alterations in melatonin under controlled laboratory conditions when humans are exposed to a magnetic field. However, melatonin levels are altered through the exposure to low frequency magnetic fields, as it has been proposed by several observational studies in occupational and residential settings, which usually differ in terms of the presence of possible confounders, the individuals' health status and their general characteristics, the exposure conditions, and the attained measurement's precisions, durations and types. The associated differences in the duration of exposure may lead to this model of conflicting results. In the laboratory studies, only one night of exposure to a magnetic field was received by volunteers. In contrast, participants in the observational studies, usually for long periods on a daily basis, received chronic exposures to such fields. The consistent measurements of each melatonin over time is considered as another related possible explanation. It is unknown if the frequent magnetic field exposures suppress the inherent stability of each measurement of melatonin over time. In conclusion, the explanation of the contrasting results obtained in laboratory studies, and not in observational ones, could be helped by the evidence for improved suppression or increased variable measurements of melatonin attained in studies with longer controlled exposures.

Keywords

Magnetic Field, Biological Effects , Melatonin.

Introduction

Melatonin is "a natural hormone (also known as 5-methoxy-N-acetyltryptamine) produced by the body (pineal gland) and is regulated by the suprachiasmatic nucleus". It make control the circadian rhythms or the wake/sleep cycle of the body. Moreover, it is depressed during the day and activated at night. Its levels of plasma are high by darkness and they are almost undetected by light. Thus, these hormones are effective indicators of the circadian rhythm or the biological clock. There are several factors included in this like the exposure's length and the individual's natural levels of melatonin. The necessary illuminance fluctuates from species to species. Other two vital factors, which determine the grade to which the clock is reset, are the wavelength and intensity of light. The blue light can well excite melatonin. Many scientific publications have proposed melatonin as "a naturally occurring free-radical scavenger and as an inducer of antioxidant enzymes during the last decade". These hormones are permeable into the brain, so they promptly cross the blood brain barrier. Therefore, they exist at significantly higher levels in the central nervous system than in the blood. Moreover, such hormones are used in the active treatment of events intractable epilepsy, because they attenuate seizures. Besides, functions of the pineal gland of activated immune cells are regulated by the immune system that interacts with these hormones. The aging process, as it was hypothesized, is helped by the decrease in the melatonin levels with age [1].

Moreover, melatonin also defined as "an effective agent that avoids both the initiation and promotion of cancer". Melatonin is also "a free-radical scavenger, as some evidence suggested". Therefore, decreased nighttime levels results in serious illnesses such as cancer. It was reported that the exposure of humans to a higher-than-normal synthetic magnetic field in association with a decrease in levels of nightly melatonin leads to a higher cancer incidence. There has been a substantial cancer incidence because of the decrease in the production of melatonin due to jet-detected lag or shift work at night. In Denmark, for an instance, a woman who has developed breast cancer after long times of nighttime working was paid compensation. In industrialiser countries, hypothesis of melatonin has been debated with respect to the considerable increase in the breast cancer incidence in current decades. The reduction of the night-time melatonin production causes the supposed risk because of exposure to houses' light at night-time, streets' light and magnetic fields associated with the electric power. Through animal experiments (rats), it has been confirmed that mammary gland tumours are quickly developed by exposure to constant light. Another study in humans, increased rates of breast cancer were shown in nightshift workers and the decreased rates of hormone-related cancer in the blind and the partly sighted and. Unlike these studies, Davis et al. [2] observed that increased hazard of developing breast cancer is not related with exposure to a



residential magnetic field. Furthermore, some other studies showed effects of low frequency magnetic fields generated by incubators on the melatonin production in young children exposures to electromagnetic field (EMF) in the a etiology of males' infertility and 2.45-GHz wireless media on modification of melatonin in mice [3].

In previous studies, the output of night melatonin was found to be unaltered by the handset emission of a mobile phone; however, there might be an influence on the onset time of melatonin. Both the human and animal melatonin effect dose as well as the administration time were examined. In infants, the development of the sleep/wake rhythm is controlled by the biological clock, which is also as the control of other biological rhythms, such as melatonin discharge, heart rate, blood pressure and body temperature. Therefore, of the biological clock development in infants is associated with the levels of melatonin that would be a useful indicator of Blood samples (serum melatonin), the melatonin metabolite 9-hydroxymelatonin, and the development of sleep/wake rhythm. Sulphate (6-OHMS) in urine can be used to determine the levels of melatonin. In infants between 06:00 and 22:00, Shinohara and Kodama [4] reported that salivary melatonin concentrations are decreased by age. Moreover, an immature sleep/wake rhythm might be indicated by the increase in morning values. In adults, melatonin levels of plasma begin to reduce after 6.00 due to the exposure to light in the morning, and they reach their lowest at 10.00 lasting the same level up until 21.00 and peak at night-light between 2.00 and 6.00. For the development of chronic diseases, including leukemia, arrhythmia, rheumatism and asthma, it takes 5-7 y of low frequency magnetic fields exposure that is considered dangerous. Moreover, that the ability of body to produce melatonin is suppressed by continued alterations in sleep patterns, as it has been proved by the World Health Organization (WHO). In experiments in organs, tissues, cells and the whole animal, melatonin has been shown to protect against harm from recognize carcinogens, such as ionizing radiation. Several variables characterize EMFs, including the magnetic field polarity and its orientation. Another study supposed that the stability of each measurement of melatonin over time has a cumulative effects of exposure to magnetic field. In those studies of people, the melatonin suppression hypothesis may be possibly because of factors other than levels of field intensity, including switching or transients, or because of the type of the field (electric rather than magnetic field). In the studies of human beings, who are exposed chronically to magnetic and electric fields, Henshaw and Reiter [5] found shore for the hypothesis of melatonin suppression. In several studies, effects of the magnetic field on the production of pineal melatonin have been investigated in volunteers exposed to magnetic field for short times. Experimental studies conducted on the suppression of pineal melatonin in people, who are exposed to chronically extremely low frequency (ELF), the influence for human fetal development, radiofrequency magnetic fields, protectiveness of melatonin with exposure to extremely low frequency magnetic fields, polarized fields and the experience of the melatonin disruption effects on the risk of miscarriage, are very essential [5].

Particularly in industrialized countries, the magnetic and electric fields exposure due to the distributions and the production of transportation of electric power "50 Hz, in Australia and Europe and 60 Hz in North America" happens in all places. Occupational and residential exposure to ELF (300 Hz) magnetic fields has several epidemiological studies which have exhibited contrasting results, while in general, they have shown a positive association with various forms of cancer, including breast cancer, brain tumors and Leukemia. However, most of population in the world are exposed to electric power in day-to-day activities. Therefore, the biological influences of electromagnetic fields and their potential results to peoples attract interests that are scientifically, and it is a very good topic to be discussed. The depth of skin is not significant at a higher frequency, so the majority of the fields' energy is absorbed adjacent to the surface of skin. For an instance, at a 2450MHz frequency, the depth of skin is 2cm, and at 10 GHz, it is 0.4cm. The magnetic fields with low frequency have several effects in this study that were examined [6].

1. Melatonin background

Melatonin is "a neurohormone secreted by the pineal gland in the brain". Melatonin levels are the gold standard for assessing the circadian rhythm, also known as your sleep-wake cycle. Melatonin supplementation is a powerful and safe way to modulate your biological clock: to consolidate your normal sleep cycle, to set your sleep cycle to a new time zone, and to enhance the efficiency of napping. Melatonin is tightly correlated with sleepiness as melatonin levels rise, so does your drive to fall asleep see figure(1).

Your circadian rhythm is "the biological clock that resides in the suprachiasmatic nucleus of the brain and drives your sleep-wake cycle". The Howard Hughes medical institute has a wonderful animation describing how this important brain region regulates your internal clock. Melatonin is thought to weaken the circadian signal promoting wakefulness - specifically, Melatonin is thought to act through direct activity in the brain as well as on peripheral blood vessels to increase heat loss, which strongly promotes sleep. Melatonin is classified as generally regarded as safe by the Food and Drug Administration. In a 2011 study, it was shown that melatonin treatment in young children can be harm over a long period of time without big deflection of the development of children with respect to sleep quality, puberty development and intellectual health signs, as compared with the public Dutch people. Demonstrating that even during sensitive periods of growth and development, melatonin consumption can be safe [7]. Effects on Cognition Two important parameters of sleep are modulated by melatonin: sleep efficiency, the effectiveness of the sleep you get, and sleep latency time required to fall asleep. Melatonin effects sleep efficiency and latency, but the evidence suggests that melatonin is most effective at improving sleep latency at night and sleep efficiency during the day. Essentially, night-time melatonin acts more strongly to

promote your desired sleep-wake cycle by reducing the time it takes to fall asleep. In contrast, day-time melatonin acts to promote sleepiness, but also improves the overall quality of sleep. Based on the melatonin cycle in figure(1), it is logical that at night, when Melatonin is rising, taking it just before bed will enhance the already rising melatonin levels, over- and above your internal clock, to help solidify your desired sleep-wake cycle. In contrast, during the day when melatonin is very low, it stands to reason that any increase in melatonin will enhance sleep, both at the levels of sleep latency and sleep efficiency [8].

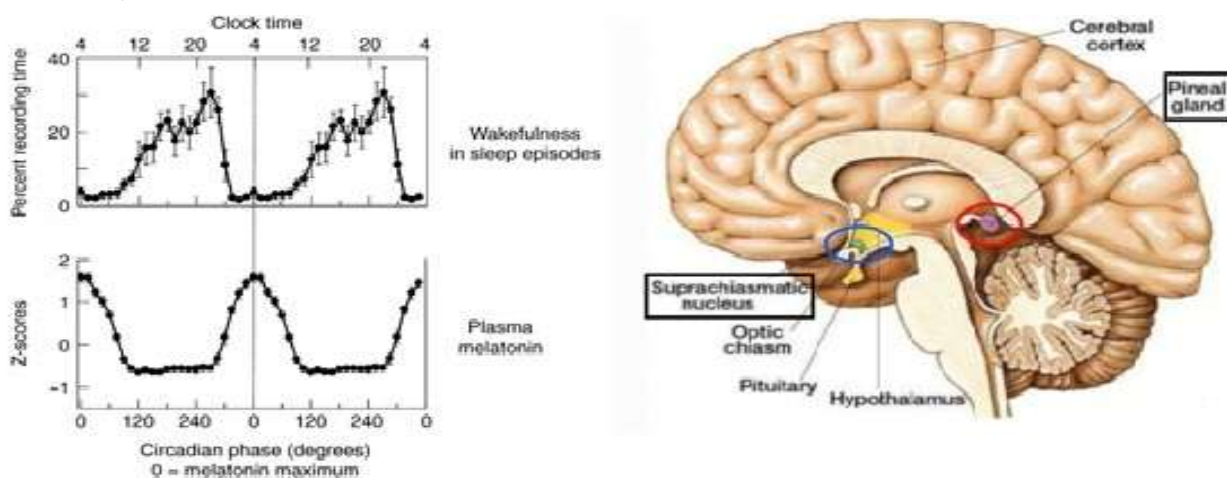


Figure (1): The left graph show melatonin peaks and the right graph show anatomy of the brain, with the pineal gland (melatonin producing part of the brain).

Another important use of melatonin, is how it can be used to resume the normal sleep-wake hormonal changes, when it is perturbed by light exposure. Many of us spend hours and hours in front of the computer, and this blue wavelength of light is particularly good at disrupting our normal sleep-wake cycle. Studies have shown that cycles disrupted by excessive light exposure, can be rescued by melatonin. So night-time melatonin may be particularly beneficial for both maintaining the desired sleep-wake cycle, and resuscitating it when environmental exposures disrupt your sleep-wake cycle. Jet lag is the result of your body's sleep-wake cycle setting itself to the new light-dark cycle as you cross through time zones. Melatonin supplementation has been shown to be a powerful method to pre-set your sleep wake-cycle. In a 2002 meta-analysis, it was shown that melatonin taken at or near bedtime at the target destination (10 pm - 12 am) significantly reduced jet lag [9]. There is great interest in the medical field to apply melatonin to the host of sleep-disorders out there, as well as diseases with associated sleep-disturbances, such as mood disorders and Alzheimer's disease. Insomnia, is diagnosed as difficulty in falling and/or staying asleep. Psychomotor performance and sleep measures are improved by melatonin in elderly patients with insomnia [4]. In another study, extralong release melatonin improvement sleeping quality and morning alertness in insomnia patients aged 55 years and elderly and had no withdrawal effects. Related to this, melatonin has been shown to reduce blood pressure in elderly individuals - particularly between 3 am - 8 am, when the risk for cardiovascular complications is highest [10].

The cancer treatment may also be helped by melatonin. While randomized control clinical trials have not shown melatonin to be effective in cancer treatment, a meta-analysis of smaller studies showed that melatonin as an assistant medication for cancer led to essential improvements in tumor reduction, 1-year survival, and reduction of radio chemotherapy related side influences. Melatonin has also been shown to reduce angiogenesis, or the formation of new blood vessels - a process critical for tumor survival. Additionally, melatonin has been shown to inhibit the metastasis of tumor cells. These evidence lend support to possible anti-cancer effects of melatonin. The biosynthetic pathway of melatonin starts from the dietary amino acid L-tryptophan, which is converted to 5-hydroxytryptophan, or 5-HTP, by tryptophan-5-hydroxylase. 5-HTP is changed to the effective hormone release by the enzyme aromatic L-amino acid decarboxylase, further converted to N-acetylserotonin by the enzyme serotonin-N-acetyltransferase (sometimes called arylalkylamine-N-acetyltransferase), and finally converted to N-acetyl-5-methoxytryptamine (melatonin) by the enzymes hydroxyindole-O-methyltransferase (HIOMT). Melatonin is also purported to play a variety of different roles in inflammation and immunity. Specifically, melatonin has been shown to reduce release of the pro-inflammatory signaling molecules interleukin-6, interleukin-8, and tumor necrosis factor. Melatonin signaling has been shown to reduce the migration of certain types of white blood cells. Melatonin has also been shown to have powerful antioxidant effects. Specifically, melatonin levels also decrease with aging, concomitantly with reduced sleep quality in older individuals [10-11].

2. Biological hypotheses relating magnetic field exposure and melatonin

Two biological hypotheses are discussed. The first one increased in amyloid beta releasing and next development of alzheimer's disease exposure to magnetic fields. The second one decreased melatonin production show to have varying unhealthy results related to alzheimer's disease and breast cancer development when exposure to magnetic fields.

3.1. Melatonin exposure to magnetic field and alzheimer's disease

Many in vitro and animal environmental studies indicate that melatonin may be protective against alzheimer's disease and thus low melatonin production may be a hazard factor for alzheimer's disease. Some studies have found that melatonin has influences which show in the following:

- Cytotoxicity and neurotoxicity of amyloid beta which including in mitochondria was decreased [12].
- Formation of beta pleated sheet structures and amyloid beta fibrils was decreased [13].
- Increased risk of alzheimer's disease by reversal of the profibrillogenic activity of apolipoprotein, [14].
- Oxidative stress in transgenic and vitro in mice models of alzheimer's disease was decreased, if given early [13], but not important if given to old mice [15].
- Increase in survival time in rats models of alzheimer's disease [13].
- Oxidative stress and of proinflammatory cytokines caused by amyloid beta rat brain was reduction [16].
- Prevalence of the brain in young and middle aged mice was decreased[17].
- Improvement of learning and memory in rat models of alzheimer's disease pathology [18], but not important in amyloid beta infused mice models [19].

Notice that transgenic mouse models of alzheimer's disease mimic, memory impairment, neuronal loss and senile plaque accumulation [20-21]. Thus, alzheimer's disease happening may be related to chronic low levels of melatonin production [21].

3.2. Melatonin exposure to magnetic field and breast cancer

See figure(2) for a diagram of the discussed relationships between extremely low frequency magnetic fields exposure and breast cancer hazard. In vitro studies related to preventing of oxidative damage. Publications have found that melatonin reduces oxidative damage and neutralizes hydroxyl radicals [22-23]. Melatonin has also been shown to act synergistically with glutathione, vitamin E and vitamin C [43] and stimulates the antioxidant glutathione peroxidase enzymes superoxide, glutathione and reductase dismutase [24]. Furthermore,

- Melatonin balances hydroxyl radicals more efficiently than does decreased glutathione peroxidase [25].
- Melatonin decreased oxidative damage to macromolecules in the presence of free radicals [26] due at least to its free radical scavenging properties [27].
- Melatonin increases the activity of other antioxidants, e.g., catalase, glutathione and peroxidase superoxide dismutase [28].
- Melatonin has defensive effects against ionizing radiation and ultraviolet [29].
- Melatonin has been found to be a more strong protector from oxidative damage than vitamin C or vitamin E [22].

Melatonin was also found in vitro to scavenge peroxy radicals more activity than vitamin E, vitamin C or reduced glutathione [30], although melatonin is not a very strong scavenger of peroxy free radicals [27].

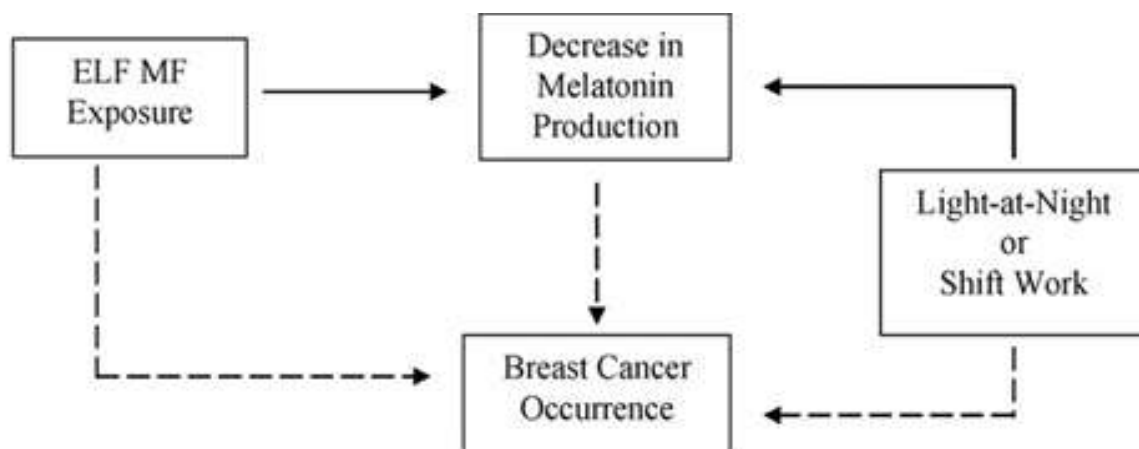


Figure (2): Extremely low frequency magnetic fields exposure causes breast cancer



3. Melatonin protects the human hemopoietic system against oxidative damage

Oxidative damage to the haemopoietic systems of humans can be highly protected by indoleamine, the suppression importance of melatonin to leukemia hazard increases. Four healthy volunteers were administered 300mg of melatonin by Vijayalaxmi et al. [31]. Directly and after 1 and 2 hours, they took blood samples to be irradiated with 1.5Gy ¹³⁷Cs gamma radiation. Chromosome aberrations and micronuclei were significantly reduced (50%–70%) in the blood sample that was taken after 2 hours in comparison with those taken directly. Free radical produced carcinogens and mutagens induce magnetic damage that could be protected by human lymphocytes which may have essential implications that were observed as a conclusion by the authors. Regarding the immediate scavenging in the cell nucleus of free radicals induced by radiations such as the radicals of hydroxyl and the cell membrane actions, the protection mechanism of melatonin was investigated by the authors. They also investigated the same protection regarding the immediate scavenging in the cytosol to activate existing enzymes of DNA repair and activate a group of genes which result in synthesizing novo proteins correlating with DNA repair. In 1999, Vijayalaxmi et al. conducted an experiment on irradiated rat with 8.15Gy gamma radiation. Mice were divided into both an untreated group and a pretreated group with 150 and 250mg melatonin. 30 days later, 45% of the untreated mice were alive, while 85% of those pretreated with 250mg melatonin were still alive [31]. Another issue has a direct relation to the suppression of melatonin and leukemia which is that melatonin has been observed to be produced by bone marrow cells. However, the exact function of melatonin in these cells is still unidentified. Therefore, melatonin may have obvious implications for leukemia in case magnetic field exposure depresses the levels of melatonin in these cells. Free radical mediated DNA damage may be enhanced by the decrease in melatonin and Childhood Leukemia S91 melatonin in the cells of leucocytes precursor that may increase the probability of developing tumors of these cells [32].

4. Results and discussion

In animals, melatonin can be suppressed by an experiment's feature which is continuous exposure required from days to weeks. Another feature is the effects, which were induced in rats at nearly low fields [33]. Melatonin can also be effectively suppressed by the electric fields' effects or by the quick onset or offset magnetic fields. In Table 1, several exposures are characterized by such features. Besides, neighborhood exposures are in general characterized by transient magnetic fields [34]. Exposures of laboratories have several drawbacks. Therefore, results from an acute laboratory expose highly differs from those in animals and in populations with long-term or chronic exposures. The exposure of volunteers to the control fields is another issue. For an instance, acute exposures over 300mT was employed by Warman et al. [35], and no melatonin suppression evidence was found. Nevertheless, their control level was given at <0.2mT and could be revealed as the region where the disruption of nocturnal melatonin is still a result of the chronic expose. Visible light, where pineal response's linearity increases from 10 - 200 lux, is paralleled for the previous issue. However, levels of melatonin are slightly influenced by higher exposures up to 50,000 lux [36]. In urine, the melatonin metabolite 6-OHMS was examined and concluded that for the suppression of melatonin, support is needed for the studies of chronic and long-term exposures. But, the conditions of exposures are different among studies conducted at different periods of a year and in broadly various places. Therefore, there must be a difficulty in comparing such studies in regard to several factors, including light-at-light, season and latitude, on which the secretion of melatonin may be affected. This proposed that further studies in human population could be helpfully conducted, but with better approved and defined protocols, see recommendations [37].

Transients, polarization and electric fields are the better characterizations of an EMF exposure. In children, EMF exposures have specific effects on melatonin as a central to future works. The synthesis of fetus melatonin in unborn humans does not happen, rather, the trans placental transfers from mothers may supply the melatonin [38]. Remarkably, the production of maternal melatonin raises during pregnancies [39]. Until 6 months after birth, significant amounts of melatonin are not produced by newborns [40]. Therefore, a relative melatonin deficiency exists in early life and throughout the fetal development. Griefahn et al. conducted a longitudinal study on 84 children; 38 girls and 46 boys [41]. They reported that the production of melatonin stays persistent in the same child throughout childhood and adolescence (from age 3 to 18) despite the huge inter differences of the child. They also reported that there is a plasma melatonin reduction in the young to a body size increase rather than to a pineal secretion decrease. However, melatonin in humans is disrupted by prolonged exposures to electric or magnetic fields associated with the electricity power, as evidence of melatonin suppression. On the other hand, several experiments conducted on animal species suggested retinal contribution as a response to magnetic fields, but other experiments concluded suggested the pineal contribution itself [42]. In the mammalian pineal gland, melatonin production has different parameters which are generally reduced by time-varying magnetic, static and pulsed fields. Moreover, melatonin levels in blood are circulated in other reports by such fields, but in another way.

The melatonin biosynthesis aspects affected by magnetic fields involve a disruption in the the melatonin formation enzyme activity, hydroxyindole-O-methyl-transferase (HIOMT), and a decrease in the rate-limiting enzyme activity in the production of melatonin, N-acetyltrans-ferase (NAT). Furthermore, there has been an increase in the concentrations of serotonin. There is a consistency among these collective changes with a decrease in the serotonin transformation to melatonin [43]. Several results have been accomplished in various studies and such parameters have not been assessed in a single experiment, though all these observations have been reported [37].

The synthesis of melatonin occurs in different organs such as the pineal gland and the bone marrow. Therefore, the results are confounded. Moreover, melatonin is in organisms and not in equilibrium. So, much higher melatonin levels are shown in a number of fluids the body, for an instance, in cerebrospinal fluids. Thus, how the serotonin conversion to

melatonin is influenced by magnetic fields within the pineal gland, which has never been precisely identified. There are many advanced theoretical explanations, such as (1) a photoreceptor in the eye detects magnetic fields which is interpreted as "light" with the melatonin resultant inhibition, (2) a field action at the biological clock level, i.e., the suprachiasmatic nuclei that results in sending a suitable signal to the pineal gland thereby either decreasing the melatonin's amount or changing its rhythm, and (3) a magnetic fields' immediate interactions with the synthesis of melatonin in the pinealocytes. There was a recent suggestion of another possible mechanism including generations of free radicals by low frequency magnetic fields, thus, decreasing the levels of melatonin because the in dole is quickly preformed to scavenge radicals. This may result in a decrease in blood and levels of tissue melatonin with no interfering with the structure of melatonin [43].

Additionally, a every small change in the Earth's DC magnetic fields is detected by birds. Moreover, fields as low as 0.084 mT can be detected by robins as shown by Ritz et al. [44], in a compliance with a resonance influence on a singlet-triplet transition in free radica reactions. Experimental support in humans for the above stated mechanisms is incomplete, while each them might be logical. There is a possible relationship between magnetic fields and cancer such as leukemia if free radical generations or levels of melatonin are changed by a magnetic field. A melatonin decrease has been associated with the initiation and progression of cancer. in several experiments, DNA was exhibited to be protected by melatonin, as an antioxidant, from oxidative damage. If it is damaged, carcinogenesis might happen and it might mutate. This probability is improved with depressed levels of melatonin. Similarly, the tumor's growth may be exaggerated by lower than normal levels of melatonin because (1) "melatonin inhibits the uptake of fatty acid growth factors by cancer cells", (2) "it inhibits telomerase activity in cancer cells thereby reducing telomere length and increasing the likelihood of cancer cells undergoing apoptosis" [45], and (2) "it inhibits synthesis of endothelin-1, a potent angiogenic factor which pro-motes blood vessel growth in tumors" [46]. However, such explanations are only probabilities which means that there is no study has found definitive links between cancer, melatonin, and magnetic field exposures. In conclusion, the hypotheses that "a magnetic field causes an increase in the risk of leukemia in children through suppression of melatonin" is reasonable but the key aspects are still need to be evaluated and examined.

Various laboratory experimental indexes for biological effects around these influces and the limit of the "International Committee of Non-Ionizing Radiation Protection" (ICNIRP) were compared in Figures (3) and (4) with magnetic fields and electric fields strengths. In the assessment of authors, over 100 scientific publications were considered. Such findings appear to comply with studies of laboratory experimental evidence of the biological effects, which has been found in the limit of ICNIRP and in the literature majority. Because of the exposure to weak EMFs, the study findings reveal a substantial disruption of melatonin-level. Health effects in people would be likely caused by such exposure. Thus, there is a need for additional study to know how the human long-term health is affected by EMFs through the disruption of melatonin. The reactions of biological systems vary due to the directions of the generated magnetic fields to the biological systems [47].

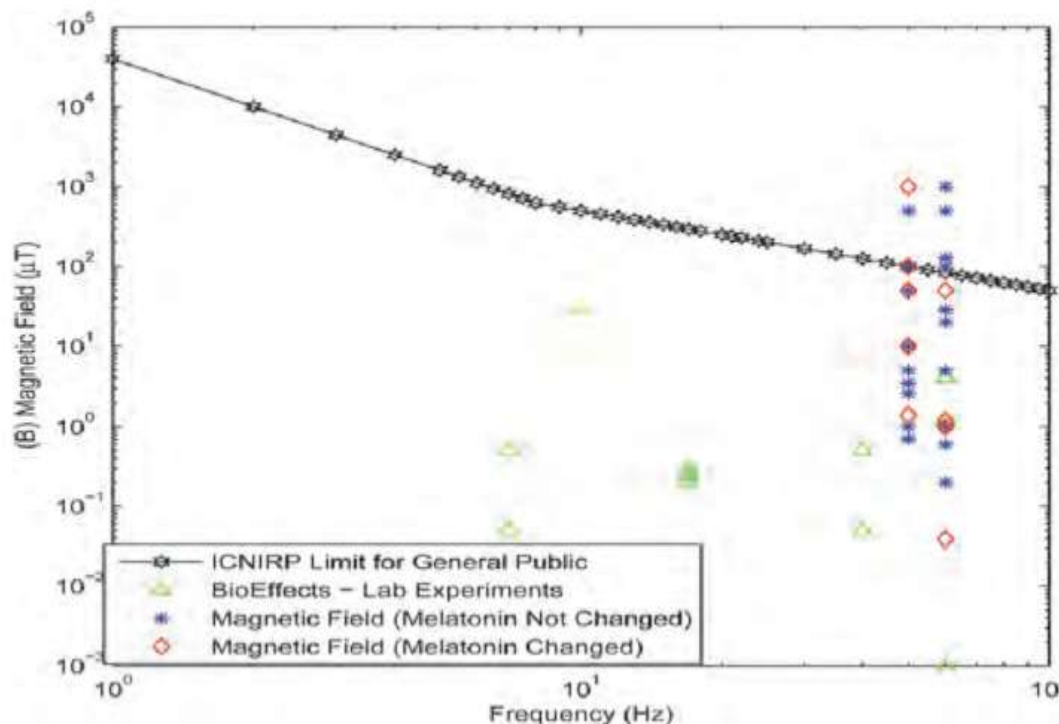


Figure (3): Melatonin production and magnetic field.

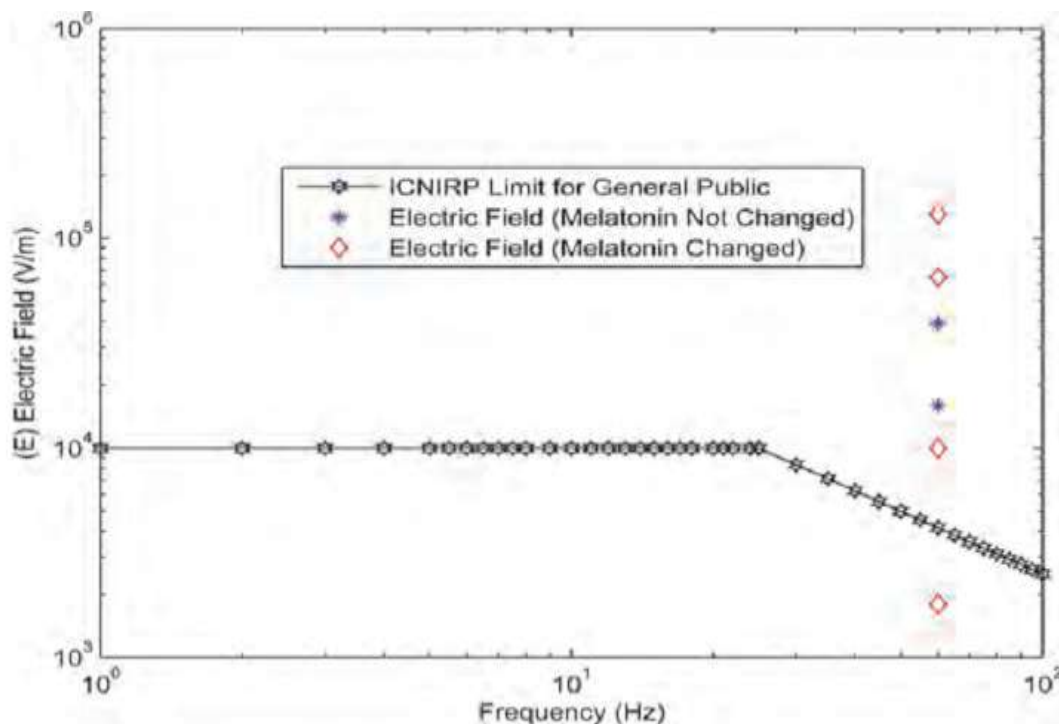


Figure (4): Melatonin production and electric field.

Moreover, the control system in various investigations was exposed to a magnetic field of the earth or to a magnetic field of DC, which is equal to the test system DC field [48]. With protecting magnetic fields of the control system, some other investigations, on contrary, have been conducted by Blackman et al. [47]. Strengths of the magnetic and electric fields are usually measured through appropriate magnetic or electric field sensors and/or meters. Every tool has environmental conditions, including humidity, temperature and light), uncertainties and limitations for measuring [49] and background EMFs which may affect these measurements [50]. The different sensitivity to ELF magnetic fields among species is one more reason for differing results of the melatonin level of plasma [51]. Irrespective to the facts, biological experiments have not been proposed to show how biological molecules can be interacted with weak fields; instead, unrealistically high amplitudes and environmental frequencies were employed for exposure. "How a large enough signal to noise ratio can be obtained to enable the living cell to detect the signal" is the key problem which all interaction models must deal with. Moreover, for a strong signal, "how the biological effects are obtained is well understood". For an instance, the body tissue will be heated by strong microwave radiations, chiefly by regulating water dipoles into rotation, and electric currents in the body will be induced by strong low frequency electric or magnetic fields. This leads to nerve excitations. On contrary, there are no normally accepted theories for an extremely weak electromagnetic signal that can clarify every the biological effect reported in the literature [52].

Health or biological effects reply mainly upon the EMFs strength, biological system, frequency, polarization and duration of exposure [50]. In biological systems, a substantial variation in the levels' response of melatonin was shown for the same frequency but with dissimilar strength of EMFs and the duration of exposure. The findings proved that characterization of biological influences by noticing only the strength ratio of the low frequency magnetic field of AC is unreliable method because in this limit, exposure period is not included, as it is in our former study [50]. In ionizing magnetic field, dose is know as "the product of dose rate and time, and is expressed in J/kg. For ionizing radiation, the risk of cancer is supposed to be dependent on the total accumulated dose". For acute influences of MF, like the death of a cell, dose-rate effects are there as it is well known. Therefore, the total dosage is given important heather in small fractions of rapid, highly intense low frequency electric or magnetic fields. On the other hand, the acute effects are ascertained in non-ionizing radiation by the radiation or fields' intensity. In most cases, progressive influences of magnetic field are not proposed to happen. The aim of ICNIRP safety limits is to defend humans against acute enflunces, including nerve stimulations and body heating, and the long term influences are not considered like risk of cancer which are not sure to be paid more attention. Regarding this, the biological effect's evidence should be acceptable because the limits of exposure can be strictly introduced only based on established experimental results [50]. Nevertheless, some experimental results go unpublished because all effects of weak fields are not shown or because the previous findings are not produced by such results. The result of the effect of magnetic field on biological systems is affected by such confirmation bias. For the analysis of experiments, the published data methods and materials should be sufficient. There is a need for mechanistic laboratory investigations so as to provide recommendations on what parameters of exposure to magnetic field wich induced in the epidemiological studies and to prove the epidemiological study results. Regardless of this, the findings need to be scientific and proved by independent studies [53].



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