Association between ELF and RF electromagnetic field and Leukemia

Majid Mahdavi[1,*] , Reza Yekta [1], Saeed Hesami Tackallou[2]

[1] Department of Biology, Faculty of Natural Science, University of Tabriz, Tabriz, Iran.
[2] Department of Biology, Garmsar Branch, Islamic Azad University, Tehran, Iran.

*Corresponding Author: email address: majid.mahdavi@tabrizu.ac.ir (M. Mahdavi)

ABSTRACT

Extremely low frequency (ELF) electromagnetic field (ELF-EMFs) are extensively employed in electrical appliances and different equipment such as TV sets, ELF-EMFs can affect biological systems by intensifying generation ROS. The changed balance between ROS generation and elimination plays a important role in a diversity of pathologic conditions. ROS levels have been observed in some hematopoietic malignancies including acute and chronic myeloid leukemia. ELF-EMFs exposure significantly reduced Nitric oxide synthase (iNOS) protein expression Lower levels of NO have been proved to exert a protective role in leukemic and melanoma cells and to prevent effector caspases by S-nitrosylation. Also ELF-EMFs can reduction melatonin production by effects on N-acetyltransferase. Melatonin is an antioxidant, impressive in protecting DNA. Transmitters emitting radio frequency electromagnetic fields (RF-EMFs) are generally not located in residential areas but some epidemiology studies showed correlation distance transmitters from residential area and leukemia.

Keywords: Extremely low frequency (ELF); Radio frequency electromagnetic fields (RF-EMFs); Leukemia; ROS (Reactive oxygen species).

INTRODUCTION

Leukemia is a group of cancer which progenitor cells in the bone marrow arised, where stem cells usually differentiate into myeloid and lymphoid progenitor cells. Lymphoid progenitor cells form mature T cells or B cells. Myeloid progenitor cells generation eosinophils, monocytes, or neutrophils. People with leukemia generate abnormal white blood cells. These abnormal cells collect in the bone marrow and inhibit the production of another consequential blood cells. Most of the problems related with leukemia are provoked by the lack of normal cells in the blood, rather than the leukemia cells themselves. Marrow precursor cells also generate red blood cells and platelets. Leukemia can be classified according to the presumed cell of origin (lymphoid or myeloid) as well as its clinical course (acute or chronic) *[1]* acute myelogenous leukemia (AML) and acute myelogenous leukemia (AML) refer to cancer of Myeloid or lymphoid progenitor cells, with fast beginning and deterioration without attacking therapy. Most childhood leukemia is each of two AML or ALL. Leukemia can be further sub-classified according to genetic alterations, surface markers, morphology cell, and other characteristics [2]. Leukemia is the sixth most prevalent malignancy in the Iran in both males and females In Tabriz (Northwest Iran) leukemia was 3.7 per 100 000 population [3] ELF-EMFs are generally employed in electrical appliances and various equipment such as mobile phones , TV sets, computers and with rising use of cell phone and personal communication service phones has necessitated a development in the number of transmitters required to support these devices. Transmitters and radio have been emitting radio frequency electromagnetic fields (RF-EMFs) in the frequency range of 10 kHz– 870 MHz. Transmitters are commonly not located in residential areas but have vast coverage areas and operate at approximately high power levels[4] Many studies showed correlation ELF-EMF (Extremely low frequency magnetic fields) and RF-EMF with leukemia[5-8] however some studies showed no relation [9-12]. International Agency for Research

on Cancer (IARC) classified Extremely low frequency magnetic fields ELF-MF as possibly carcinogenic (group 2B). The IARC assessment was driven by a two-fold rise in risk of childhood leukemia (CL) among the exposed above 0.3–0.4 μT observed in two partially overlapping pooled analyses of studies published up to 1999 [13, 14]. A pooled analysis of seven studies published later on (up to 2010) widely replicated the earlier findings [15] Recent important reviews of the evidence achieved that there is still limited evidence for an correlation between CL and ELF-MF; the correlation is dependable and apparently specific, but its causality is still ambiguous [16, 17]. So without further improvements in exposure evaluation and knowledge of biological mechanisms epidemiological studies will not be able to help further insights on the topic [18, 19] however several mechanism suggested [20, 21]. In urban areas, most RF-EMF in the environment is produced by local radio and television stations, with smaller portion from cell phone communications and emergency-services mobile [22]. So, these transmitters have created public concern about the health effects of RF-EMF. Some studies reported distance transmitters from residential area [23]. albeit, another studies showed no relation[24].

Leukemia in Relation to Distance from Power Lines

Extremely low frequency (ELF) electromagnetic fields (EMFs) are widely present in modern society and in the last 20 years the interest about the probable effect of ELF-EMFs on human health. Epidemiological studies, designed to confirm whether EMF exposure may be a potential risk factor for health[25]. Usually ELF region of the electromagnetic spectrum is defined by frequencies from 3 to 3000 Hz [26] These fields are produced by electrical devices (such as hair dryer, TV, joy sticks, video game controllers, i.e.), high tension electrical distribution networks, from residential and occupational sources and by power lines [27]. Power lines are main source for production ELF-EMF [28]. The International Agency for Research on Cancer has classified extremely low-frequency magnetic field exposure as being possibly carcinogenic to human (Group 2B; IARC, 2002) [6]. The investigation of an correlation between raised exposure to residential extremely-low frequency electromagnetic fields (ELF-EMF) and childhood leukemia [8, 16]. Albeit some studies showed that there is no significant risk [10, 29, 30] many studies have been demonstrated distance from overhead power lines can association with childhood leukemia. For children living close overhead power lines and exposure to ELF-MF levels of at least 0.3–0.4 μT was significantly related with an increased frequency of childhood leukemia [28, 31]. Many epidemiologic studies have reported relation between measures of power-line electric or magnetic fields (EMFs) and childhood leukemia [1]. For example, in the Seven studies in Germany , Japan, Brazil , United Kingdom , Tasmania, Italy with a total of 10865 cases and 12853 controls and analysis 24-h magnetic field measurements or estimated fields in residences. Show risk leukemia riased with increase in exposure, but the assessment were imprecise [7]. The odds ratios for exposure categories of 0.1–0.2 mT, 0.2–0.3 mT and 0.3 mT, compared with 0.1 mT, were 1.07, 1.16 and 1.44, respectively [31].The odds ratio (OR) is a measure of relation between an exposure and an result. The OR represents the odds that an result will occur given a particular exposure, compared to the odds of the result occurring in the absence of that exposure. Odds ratios are most usually used in case-control studies, although they can also be used in cross-sectional and cohort study designs as well [32].

OR=1 Exposure does not affect odds of result

OR>1 Exposure related with higher odds of result

OR<1 Exposure related with lower odds of outcome

So odds ratios showed risk factor for childhood leukemia. Whatever distance lesser from nearest power line risk factor for childhood leukemia riased [31]. Exposures to ELF-EMF higher level 0.4 μT in the occupational environment may increase the risk of leukemia in adults [33].

Correlation between Watching TV and Playing Video Game with Child Leukemia

EMFs produced by television set and/or the hardware (i.e., joy sticks, video game controllers, power transformers) Some epidemiologic studies have reported relation between childhood leukemia risk and mothers' reports of their children's television (TV) viewing [34] usage of TV sets for playing video games [35]. Although, either

epidemiologic studies achieved any direct measure of magnetic or EMFs exposure related with the use of this appliance [35]. The VLF and ELF exposure levels so determined were 0.0091 and 0.0016 mT, respectively, for children watching TV programs and 0.023 and 0.0038 mT, respectively, for children playing video games and ELF levels with TV sets turned off were 0.10 and 0.0027 mT, respectively [35]. The ELF produced by TV sets are likely comparable to or smaller than normal residential ambient levels at position where children sit while watching them [35]. So it may so risk factor for childhood leukemia as respects distance children from TV are less and Viewing TV or playing game in a long time. In epidemiologic studies ELF exposure evaluation are most important tasks so with development of EMF measurement appliance can better determine relation between ELF-EMF and leukemia.

MECHANISM

Mechanism affects ELF-EMFs on leukemia

The molecular mechanism through which ELF-EMFs can impress cellular behavior is still unknown. A theory is that ELF-EMFs could intervene with chemical reactions involving free radical generation [20] . Under physiologic conditions, cells control redox equilibrium through generation of ROS/RNS and antioxidant molecules. The changed equilibrium between ROS production and elimination plays a important role in a diversity of pathologic conditions including aging, neurodegenerative diseases and cancer increased ROS levels have been recognized in several hematopoietic malignancies including chronic and acute myeloid leukemia. Oxidative stress is a condition arising from an increased generation of reactive oxygen species (ROS) related with a reduced antioxidant capacity of the cell ROS are constantly producted in aerobic cells by the deficient diminution of molecular O_2 to H_2O during mitochondrial oxidative phosphorylation, as well as during a number of processes such as infections , Inflammation, chemical and mechanical stresses, exposure to UV and to ionizing irradiation [36].

The regulation of oxidative stress by ROS has been shown to be essential for the maintenance of the capacity of hematopoietic stem cells to self-renew [37]. ROS play an important role in the organizing of signal transduction causing monocytic, neuronal, or erythroid differentiation as well [38]. Evidence for chronic oxidative stress has been found in some hematopoietic malignancies such as myeloid leukemia. ELF-EMFs exposure significantly reduced Nitric oxide synthase (iNOS) protein expression [20]. Nitric oxide synthase which catalyze the conversion of the amino acid L-arginine to L-citrulline in a NADPH and O_2^- dependent process and produced Nitric oxide (NO). NO is a extremely reactive free radical that acts as inter/ intracellular mediator in pathological and physiological processes NO is part of anti-oxidative defenses by its diffusion-controlled reaction with O_2^- [39]. This inhibits the reductive chemistry of O_2^- and prevents H_2O_2 generation. Lower levels of NO have been determined to exert a protective function in leukemic and melanoma cells and to inhibit effector caspases by S-nitrosylation. On the other hand, in the excess of the superoxide radical, peroxynitrite are generated in the interaction with NO. The resulting nitrosative stress causes the inactivation of important cellular enzymes by the nitrosylation of thiol groups and iron-sulfur clusters, which directly influence redox-sensitive transcription factors implied in carcinogenesis or modulates availability of promoters via increased DNA methylation or histone deacetylation [40]. Also ELF-EMFs exposure can decrease levels of catalase (Figure.1) [20]. It catalyzes the decomposition of hydrogen peroxide to water and oxygen. It is a critical enzyme in protecting the cell from oxidative stress by ROS. Activation growth factors, including interleukin-3, stem cell factor and thrombopoietin, have been shown to be related with variation in the levels of hydrogen peroxide (H_2O_2) [41, 42].

However it is known that intracellular redox condition modulates Monocyte chemoattractant protein-1 (MCP-1) expression [43]. MCP-1 is one of the key chemokines that regulate infiltration and migration of macrophages / monocytes [44].

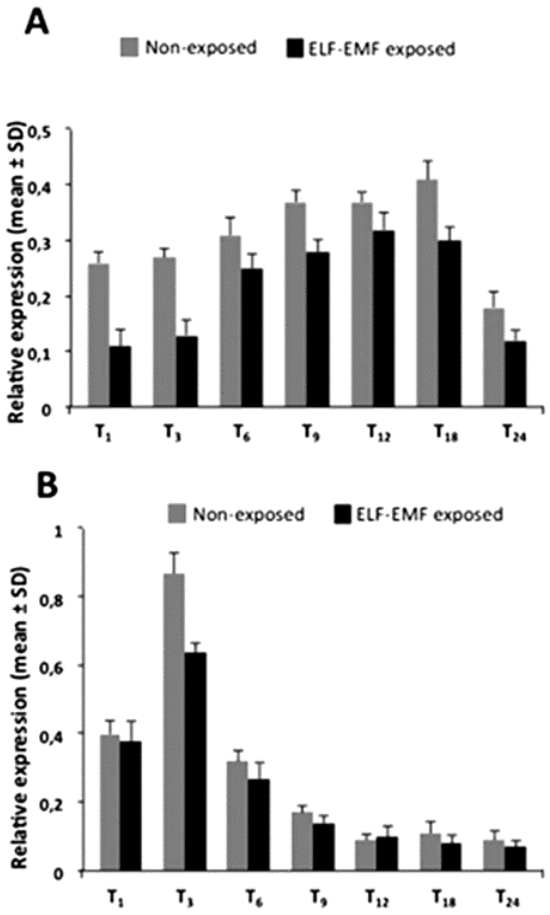

Figure 1. Comparative expression of iNOS (A) Catalase (B) and protein expression in ELF-EMF-exposed or not [20].

Melatonin

Melatonin, a ubiquitously acting hormone derived from the pineal gland, represents a marked circadian rhythm in the blood of mammals with high levels constantly being related with the dark phase of the light: dark cycle [45]. The light: dark environment regulates pineal melatonin synthesis via the eyes in mammals. Light, considerable the retinas activates a series of neurons that project from the eyes to the suprachias matic nuclei (SCN) of the hypothalamus; the neural pathway connecting the retinas to the SCN is referred to as the retinohypothalamic tract. Light detection by the retinas results in the prohibition of neurons in the SCN which eventually project, via a multi synaptic pathway, to the pineal gland. During darkness the prevention influence on the SCN is lifted, at which time the nuclei signal the pineal gland to generation and secrete melatonin [21]. The circadian rhythm of melatonin generation (high melatonin levels at night and low during the day) in the mammalian pineal gland is altered by visible portions of the electromagnetic spectrum [46]. Non-visible electromagnetic fields effect on retinas in particular have been hypothesized to serve as magnetoreceptors with the changed melatonin cycle being a result of a disorder in the neural biological clock, i.e., the suprachiasmatic nuclei (SCN) of the hypothalamus, which produce the circadian melatonin rhythm (Figure. 2) [45].

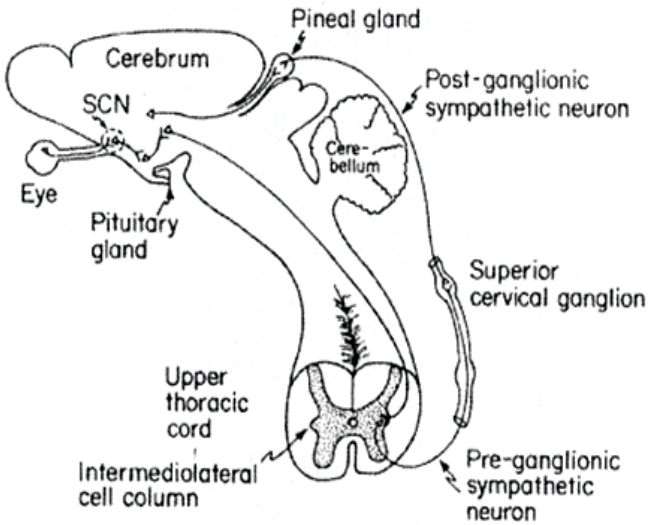

Figure 2. Neural relation between the eyes and the pineal gland. Retinas to serve as magnetoreceptors [47].

melatonin biosynthesis which have been reported to be affected by magnetic fields include a decline in the activity of the rate-limiting enzyme in melatonin generation, that is, N-acetyltransferase (the rate limiting enzyme in pineal melatonin production), and a suppression in the activity of the melatonin-forming enzyme, hydroxyindole-O methyltransferase (the melatonin forming enzyme) and pineal and blood melatonin concentrations were depressed and rise in pineal levels of serotonin (SHT) and S-hydroxyindole acetic acid (SHIM) were also seen in these glands; these rise are constant with a depressed melatonin synthesis (Figure. 3) [45, 48, 49].

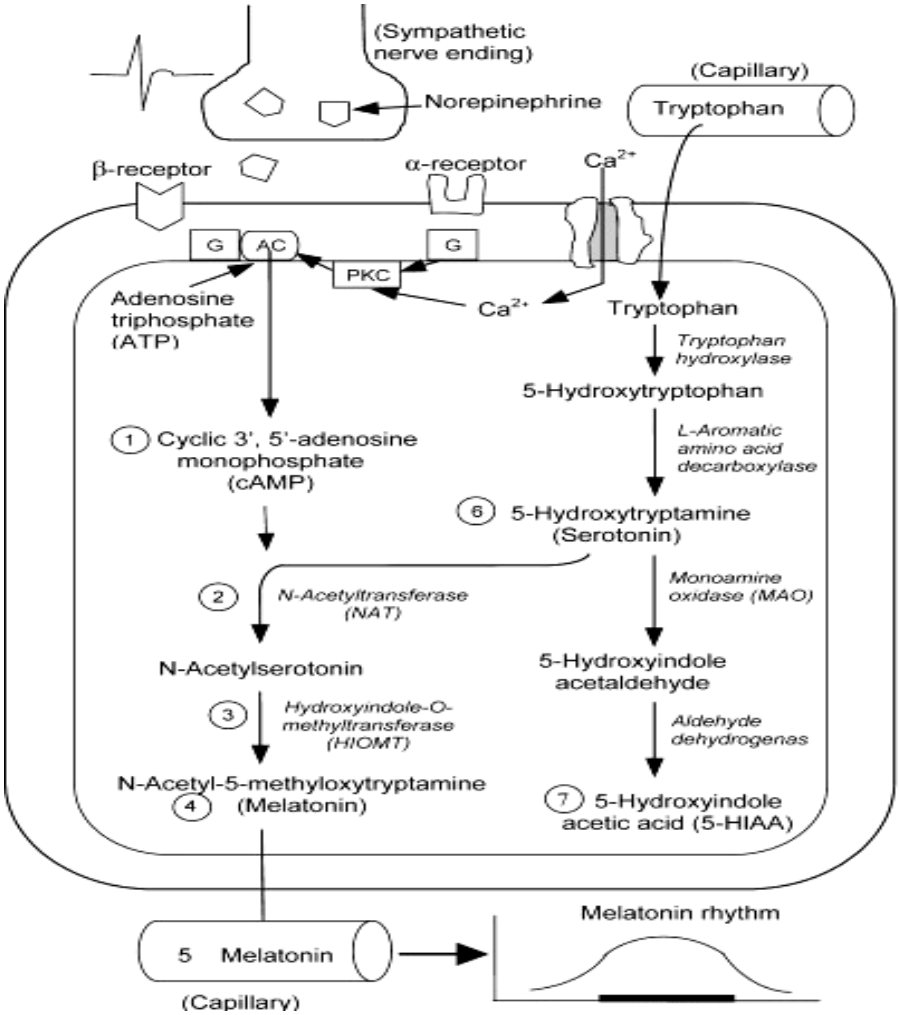

Figure 3. Diagrammatic interplay of the postganglionic sympathetic neurons with the mammalian pinealocyte and the melatonin synthetic pathway. The items numbered 1-7 are those components that have been reported to be changed by electromagnetic field exposure in animals. Numbers 1-5 identify components which reportedly decrease, while items 6 and 7 increase [47, 48, 50].

Melatonin is an antioxidant, effective in protecting membrane lipids, nuclear DNA, and cytosolic proteins from oxidative damage [51]. It has been reported to change the activities of enzymes which enhance the total antioxidative defense capacity of the organism and more effective than either vitamins E or C in vivo [52, 53]. A difference of bone marrow cells have been shown to generate melatonin [54-56] so potential importance of melatonin prevention to leukemia risk arises from the observation that the indoleamine is highly suppression of oxidative

damage to the human haemopoietic system [57, 58]. A decline in Melatonin and Childhood Leukemia melatonin in the leucocyte precursor cells would be expected to raise free radical-mediated DNA damage, so increasing the likelihood of these cells expanding tumors. As well as, showed that in pregnant women, serum melatonin shows a diurnal rhythm which enhance after 24 weeks pregnancy until term, and levels are relevanted to the feto-placental unit.[59] melatonin has been shown to be highly protective of oxidative damage to the fetus [60-62], so exposure EMF can effects on fetus.

Association Between Transmitters Distance From Residential Area and Statistical Leukemia

For many decades, radio and TV broadcast stations have been emitting radio frequency electromagnetic fields (RF-EMFs) in the frequency range of 10 kHz to 870 MHz. Amplitude modulated (AM) transmitters are generally not located in residential areas but have vast coverage areas and operate at relatively high power levels (Figure 4) showed vast coverage areas and multiple emitting radio frequency electromagnetic fields (RF-EMFs) from different transmitters which have overlap in Tabriz (Northwest of Iran), so can result in a high level of population exposure [4]. Also some townships of around Tabriz transmitters location are inside the residential area (Figure 5).

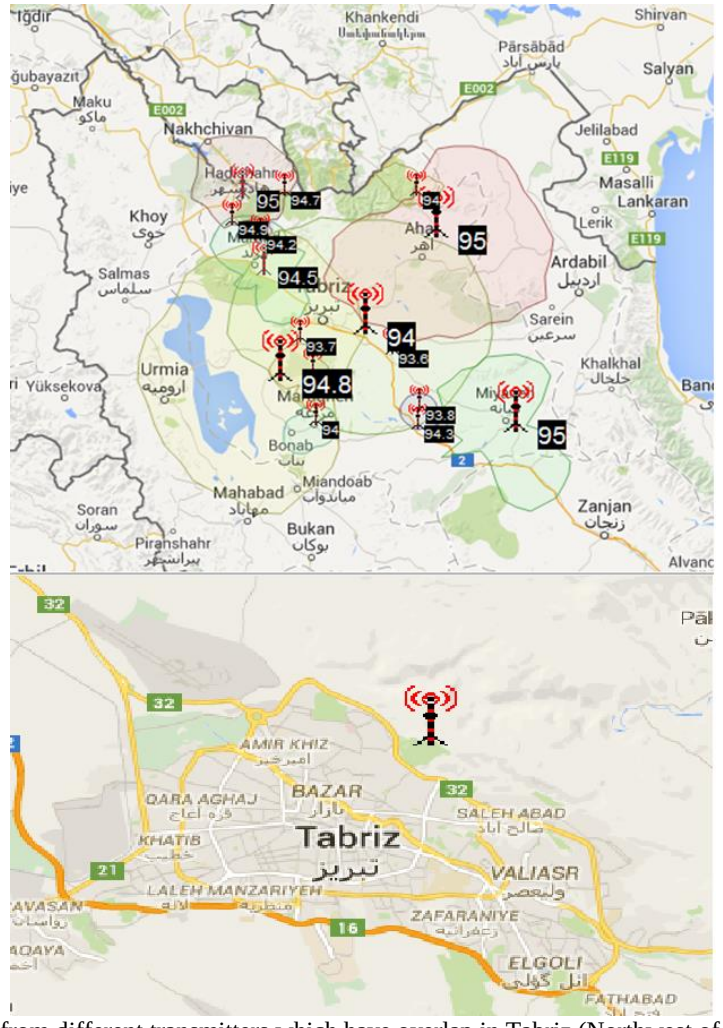

Figure 4. Radio frequency from different transmitters which have overlap in Tabriz (Northwest of Iran) (http://fmscan.org/).

Figure 5. Bostan Abad and Maragheh are townships of around Tabriz transmitters location are inside the residential area (**http://fmscan.org/**).

The analysis several studies demonstrate risk factor for adult and childhood leukemia increased who located in

nearby TV or radio transmitter as compared with those resided farther form it [11, 23] [63]. For example in study of South Korean the odds ratio for all types of leukemia was 2.15 among children who located within 2 km of the nearby AM radio transmitter as compared with those located more than 20 km from it [23]. though, other studies reported no association [11, 24]. Annual frequency of leukemia was 3.7 per 100 000 population in Tabriz Over the study period, the annual frequency of leukemia in the region increased from 3.9 per 100000 population [3].

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