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Effects of short term and long term Extremely Low Frequency Magnetic Field on depressive disorder in mice: Involvement of nitric oxide pathway

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ABSTRACT

Aims: Previous reports on the possible effects of Extremely Low Frequency Magnetic Fields (ELF MF) on mood have been paradoxical in different settings while no study has yet been conducted on animal behavior. In addition, it was shown that ELF MF exposure makes an increase in brain nitric oxide level. Therefore, in the current study, we aimed to assess the possible effect(s) of ELF MF exposure on mice Forced Swimming Test (FST) and evaluate the probable role of the increased level of nitric oxide in the observed behavior.
Main methods: Male adult mice NMRI were recruited to investigate the short term and long term ELF MF exposure (0.5 mT and 50 Hz, single 2 h and 2 weeks 2 h a day). Locomotor behavior was assessed by using open-field test (OFT) followed by FST to evaluate the immobility time. Accordingly, NΩ-nitro-L-arginine methyl ester 30 mg/kg was used to exert anti-depressant like effect.
Key findings: According to the results, short term exposure did not alter the immobility time, whereas long term exposure significantly reduces immobility time ($p < 0.01$). However, it was revealed that the locomotion did not differ among all experimental groups. Short term exposure reversed the anti-depressant like effect resulting from 30 mg/kg of NΩ-nitro-L-arginine methyl ester ($p < 0.01$).
Significance: It has been concluded that long term exposure could alter the depressive disorder in mice, whereas short term exposure has no significant effect. Also, reversing the anti-depressant activity of L-NAME indicates a probable increase in the brain nitric oxide.

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1. Introduction

Nowadays, human beings are exposed to Extremely Low Frequency Magnetic Fields (ELF MF) both from natural and artificial sources. The sun, the earth and human body emit magnetic fields (MF). Power plants transport power lines as well as all electrical appliances which are among ELF producers. All electric utensils such as laptops or cell phones working with electric circuit in our environment produce MF with frequency ranging from 50 to 60 Hz depending on the existing electric frequency affecting the biologic systems nearby. These MFs are ubiquitous in modern society. The more exposure to ELF due to modernization, the more concern arises on their safety. The adverse or beneficial repercussions of these ranges of MFs have been revealed in different fields of health [9,11]. One possible mechanism in behavioral effects of ELF is nitrergic system. For example, the inhibitory effect of ELF on anti-nociception in land snail was reversed by NO synthase inhibitor in a previous study (NΩ-nitro-L-arginine methyl ester or L-NAME) [19].

Major depressive disorder is one of the most common psychiatric disorders with substantial impacts on morbidity and mortality [20]. The latest World Health Organization global health risk report points out that depression is the leading cause of failure due to disability [24]. Depression has a remarkable impact on economy, especially in modern societies in which the chronic diseases like cancer are increasing [14,22].The results of former studies of ELF effects on mood have been paradoxical in different settings. The first study on the possible psychiatric ripple effects of ELF was conducted in England suggesting that the rate of perpetrating suicide among people who were exposed to intense MFs at their home, is greater [29]. Although this study was methodologically limited, another similar study revealed a relation between the proximity to MFs and severity of depression [27]. Despite the therapeutic effect of weak variable MFs in the treatment of depression [32], there have been multiple reports of association between ELF and suicide attempt among electric utility technicians [3,34]. Conversely, there have been some reports revealing no association between depression and working in electrical fields [33]. For instance, in the

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survey conducted by Nevelsteen et al., acute exposure to 50 Hz MFs (400 μT(rms)) did not significantly alter the mood in male volunteers [25]. However, trans-cranial magnetic stimulation (TMS) of brain in humans has shown antidepressant effects in different studies [1,18]. Also, TMS was shown to decrease the immobility time of rats in Porsolt's model of depression known as Forced Swimming Test (FST) [31]. Moreover, electroconvulsive therapy (ECT) at 60 Hz has shown that it could reduce immobility of rats in FST, probably with the same mechanism of TMS [4,35]. In this regard, Kheifets et al. in 2009 pointed out the necessity of more researches on ELF exposure assessment [21].

With the advent of the third millennium, Ahlbom et al. concluded that inconsistency of the results of evaluating ELF effects on depression made the interpretation difficult [2] and since researches on the possible effects of ELF on human raises ethical issues, animal model studies remain a possible reliable alternative. Thus, prior to the present study, no animal study has been conducted to survey the possible role of ELF MF on depression as far as we are concerned. In the present investigation, the effect of ELF on mice depressive behavioral model has been assessed by using Forced Swimming Test (FST) as a model commonly used to assess depression-like state in rodents.

2. Materials and methods

2.1. Animals

72 male adult NMRI mice weighing 20–30 g from Pasteur Institute of Iran were used in the present research. There were 8 groups and the number of animals used in each group was 9; short term exposure, short term sham exposure, long term exposure, long term sham exposure, short term exposure/L-NAME, short term exposure/saline, sham exposure/L-NAME and sham exposure/saline groups. Because of limited exposure site in the generator, animals of each group were divided into groups of four to five members in a cage in order to be exposed to the ELF MF or sham exposure. The environment temperature maintained at 20–22 °C under a 12 h regular light/dark cycle (lights on at 07:00 am). Animals had free access to food and water except for short period when removed from their cages at test time. All behavioral experiments were conducted between 12:00 pm till 18:00 pm. All experiments and manipulations were performed in compliance with the animal care and ethical committee of the institution (Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences) guidelines for animal care and use. This study was approved by the Ethics Committee of Tehran University of Medical Sciences.

2.2. ELF exposure

ELF exposure set up was a modified form of previously described method [9,23]. In order to produce a field with 50 Hz frequency and the RMS value of 0.5 mT, a pair of Helmholtz coils was set with winding embedded in a plexiglass frame. The device for the exposure of animals consisted of two pairs of coaxially arranged Helmholtz coils. The diameter of each coil is 91.4 cm; the distance between the coils in the pairs is 50 cm and there are 60 turns of 2.5 mm copper wire oriented along the vector of the geomagnetic field (GMF). The coils were connected in a series to 220 V AC power supply through variable transformer. The centrally horizontal MF was homogenous in a cage made of plexiglass (a non-magnetic material). Sham exposure group was placed in the same plexiglass while the coils were off, being exposed to the local geomagnetic field. The homogeneity in the plexiglass was determined by using a gauss meter (Lake Shore Model 410). The coils were connected to a wave form generator (GW Instek SFG-1000 Series, South Korea) to regulate the frequency and intensity. A temperature probe has been fused to the coils and reported the temperature interactively. The temperature during the exposure did not exceed over 27 °C. As it is shown in Fig. 1a, short term exposure and FST were conducted within 2 h and 45 min, respectively. After the short term exposure, long term exposure was performed 2 h per day for 2 weeks and each week for 6 days (one day break), and locomotor activity and FST were taken 45 min after the last exposure.

2.3. Drug and treatment

NΩ-nitro-L-arginine methyl ester (L-NAME) (Sigma, St. Louis, MO, USA) was used as a nonspecific NOS (Nitric Oxide Synthase) inhibitor diluted in physiological saline and administered intraperitoneally. There were four groups and there were 9 mice in each group. 2 groups have been treated with L-NAME 30 mg/kg and another 2 groups have been treated only by normal saline as control group. Therefore, we had short term exposure/L-NAME, short term exposure/saline, sham exposure/L-NAME and sham exposure/saline groups. According to the diagram in Fig. 1b, L-NAME (30 mg/kg) or saline in related groups was immediately administered after the exposure and the tests were conducted after 45 min. According to the literature, dose of 30 mg/kg was used to show anti-depressant like effect [13]. Each group was individually entered in locomotor test and was subjected to FST and each mouse was tested for once.

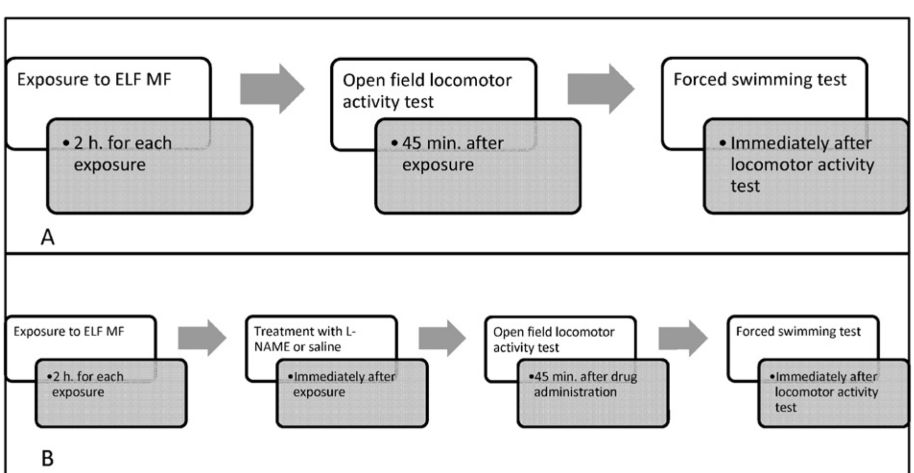

Fig. 1. Diagrams of procedure without drug treatment (A) and with drug treatment (B).

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