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Research report

Stress-related endocrinological and psychopathological effects of short- and long-term 50 Hz electromagnetic field exposure in rats

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ABSTRACT

It is believed that different electromagnetic fields do have beneficial and harmful biological effects. The aim of the present work was to study the long-term consequences of 50 Hz electromagnetic field (ELF-EMF) exposure with special focus on the development of chronic stress and stress-induced psychopathology. Adult male Sprague–Dawley rats were exposed to ELF-EMF (50 Hz, 0.5 mT) for 5 days, 8 h daily (short) or for 4–6 weeks, 24 h daily (long). Anxiety was studied in elevated plus maze test, whereas depression-like behavior of the long-treated group was examined in the forced swim test. Some days after behavioral examination, the animals were decapitated among resting conditions and organ weights, blood hormone levels as well as proopiomelanocortin mRNA level from the anterior lobe of the pituitary gland were measured. Both treatments were ineffective on somatic parameters, namely none of the changes characteristic to chronic stress (body weight reduction, thymus involution and adrenal gland hypertrophy) were present. An enhanced blood glucose level was found after prolonged ELF-EMF exposure ($p = 0.013$). The hormonal stress reaction was similar in control and short-term exposed rats, but significant proopiomelanocortin elevation ($p < 0.000$) and depressive-like behavior (enhanced floating time; $p = 0.006$) were found following long-term ELF-EMF exposure. Taken together, long and continuous exposure to relatively high intensity electromagnetic field may count as a mild stress situation and could be a factor in the development of depressive state or metabolic disturbances. Although we should stress that the average intensity of the human exposure is normally much smaller than in the present experiment.

1. Introduction

Along technological advance using more and more electrical devices, exposure to extremely low frequency (50 Hz) electromagnetic field (ELF-EMF) has significantly been enhanced in both intensity and duration and seems to affect public and occupational health more and more [36,38]. Contrary to high frequency and high energy ionizing electromagnetic radiation, the harmful features of ELF-EMF have not been proven unambiguously although biological effects were demonstrated in many studies of different sort [24]. 50/60 Hz electromagnetic field is generated by the power lines, transformers and electrical devices induced with current flow, thus it can be found in our living environment, which has raised some concerns about the effects of ELF-EMF on human health [38].

Over the past decades, experimental data have shown that ELF-EMF can act on the emotional state of people and on the anxiety-related behavior of animals. For example, epidemiological studies suggested an association between chronic ELF-EMF exposure and depression [5,51]. It was also reported that residential exposure to ELF-EMF could increase trait anxiety in women [10]. Moreover, repetitive transcranial magnetic stimulation (rTMS), a magnetic field exposure used for therapeutic purposes, was reported to cause anxiety in normal volunteers [22]. In accordance with this, Isogawa et al. [28,29] observed an anxiogenic effect of rTMS in rats on the elevated plus maze (EPM). Although results from behavioral studies are rather ambiguous, according to some studies, ELF-EMF enhanced the anxiety-like behavior in rats by increasing the time spent with thigmotaxis (tendency to stay close to the sidewall of the open field box), by increasing the frequency of grooming behavior in the open field test [15,38], and by decreasing the open arm entries and the time spent in the open arm or on the central platform of the EPM [15,62]. The precise mechanisms of alterations in the anxiety level caused by ELF-EMF exposure are not fully understood.

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It is well known that activation of the central corticotropin-releasing factor (CRF) system and the glucocorticoid secretion can evoke negative emotional state and can potentiate fear- and anxiety-related behaviors [39]. Therefore, it is reasonable to speculate that elevation in the anxiety level may be attributed to the stimulating effect of ELF-EMF on the hypothalamic–pituitary–adrenal (HPA) system function. To our best knowledge, the effect of ELF-EMF exposure on the HPA axis function has not yet been studied extensively. Some reports suggest that long-term ELF-EMF exposure may elevate the plasma corticosterone level and the mean lipid volume in the zona glomerulosa of adrenal cortex in rodents [18,46]. These data suggest that the ELF-EMF exposure may act as a chronic stressor [18]. According to another study [70], however, chronic ELF-EMF exposure was accompanied by markedly depressed level of circulating corticosterone in young chickens. Based on the above-mentioned studies, we hypothesized that long term, permanent ELF-EMF exposure would result in a chronic stress state accompanied by the permanent activation of HPA axis with consequent anxious and depressive-like behavior.

Activation of the HPA axis is a fundamental component of stress-adaptation and survival. It leads to an enhanced secretion of CRF from the hypothalamus provoking the splicing of adrenocorticotropin (ACTH) from proopiomelanocortin (POMC) precursor in the anterior lobe of the pituitary gland. ACTH triggers the secretion of glucocorticoids from the adrenal cortex. Overall functioning is controlled by several negative feedback loops (for an overview, see [16,64]). The consequences of the physiologic response are generally adaptive in the short run but can be damaging when stress is chronic and long lasting [21,42,56]. The chronic stress-induced inhibition of weight gain [32,44] can be explained by CRF rises, as CRF is an anorexigenic molecule, therefore it reduces food intake and body weight [14,37,41,71]. The plasma ACTH level was found to be unchanged in different chronic stress situations, but the more proximal level of the axis (POMC mRNA level) showed enhanced activity [72]. In animal models, exposure to chronic stress increases adrenal weight [44,55] due to resting corticosterone/cortisol hypersecretion [2,3,59,71]. Studies have found complex and bi-directional regulatory interactions between the immune and HPA systems [6]. Due to persistent excess of glucocorticoids in chronic stress state, cellular immunity is suppressed [7,19] and thymus is involuted in rats [20,63]. Corticosterone increases plasma glucose level, too; e.g. chronic restraint stress caused permanent increase in fasting basal plasma glucose levels [71]. What is more interesting, stress may induce diabetes mellitus in humans [54,60] or different kinds of stressors could evoke or inhibit type 1 diabetes in different experimental models of the disease [13,26]. Exposure to chronic stress in rodent-models induces several emotional or behavioral changes including anxiety, anhedonia, enhanced fear, and depression-like states [8,9,17,68,69], probably due to neuronal atrophy in the hippocampus [43,67] and to impaired glucocorticoid receptor function in the forebrain [11] caused by the enhanced glucocorticoid secretion.

It is not yet clear, however, how mood changes develop in time and how the length of ELF-EMF exposure affects short- and long-term stress adaptation. The aim of our present work was, therefore, to study the consequences of short- and long-term exposure to ELF-EMF (durations of 5×8 h and 4–6 weeks, respectively, 50 Hz frequency, 0.5 mT intensity) on anxiety- and depression-related behavior of rats in connection with the development of chronic stress state. Anxiety was studied in EPM test both after short- and long-term EMF exposure, respectively, whereas depression like behavior of the long-exposed group was examined in the forced swim test (FST). Finally, to assess chronic stress-related endocrine changes, changes of the adrenal gland and thymus weights as well as of the body weight of the animals, blood hormone levels of ACTH and corticosterone, POMC mRNA level from the pituitary gland, and blood glucose and haematocrit levels were measured both after short- and long-term EMF exposure.

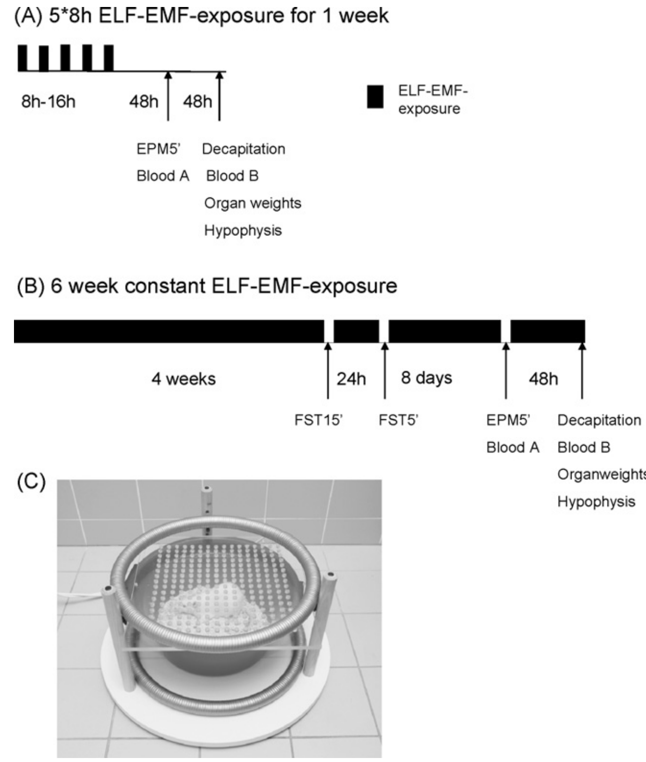

Fig. 1. Scheme of *Exp. 1* (A) and *Exp. 2* (B). *Abbreviations*: EPM = elevated plus maze; Blood A = blood samples from the tail for measuring ACTH and corticosterone level after EPM test; Blood B = blood samples after decapitation for measuring basal ACTH and corticosterone level, blood glucose level and haematocrit; Organ weights = measuring the weight of the thymus and the adrenal gland; Hypophysis = taking out the pituitary gland for the ACTH precursor POMC mRNA level determination. FST = Forced swim test. Numbers indicate the length of the procedure. (C) Helmholtz-coil apparatus for the ELF-EMF exposure with the plastic box containing rats between the coils.

2. Materials and methods

2.1. Animals

Subjects were male Sprague–Dawley rats weighing 300–370 g in *Group* 5×8 h and 120–140 g in *Group Chronic* at the start of the experiment (EGIS Pharmaceuticals Budapest, Hungary). Each group consisted of 8 rats, alltogether 32 animals were used. Rats were kept in a 12:12 h day–night schedule (lights on at 7:00 a.m.) under normal laboratory conditions (temperature: 22 ± 2 °C). Standard laboratory chow and tap water were available *ad libitum*. The experimental design had been approved by the Eötvös Loránd University Animal Use and Care Committee and by the Hungarian National Animal Health Care Authority and was in accordance with regulations set by the European Communities Council Directive of 24 November 1986 (86/609/EEC).

2.2. Apparatus

2.2.1. Device for electromagnetic field exposure

ELF-EMF was generated by a standard Helmholtz-coil apparatus. Two round coils were used, spaced apart at a distance equal to their radii (21 cm) on a common axis, with equal currents flowing in the same direction (Fig. 1C). Helmholtz coils provide a fairly homogenous field in the space between them. The coils were constructed of glaze-insulated copper wire (d = 1.4 mm) and had 240 turns (DC resistance was 2.9 Ω). 50 Hz EMF frequency was generated by sinusoidal current (1.6 A in each coil) at the output of the circuit driven by a 230 V, 180 VA adjustable thoroid-transformer. EMF was measured by a hand-held Electric and Magnetic Field Meter (Maschek-ESM-100) and the value of the magnetic field was fixed at 0.5 ± 0.025 mT. The electric gradient was between 525 and 575 V/m. The ambient background level of the magnetic field was <0.01 mT. Subjects were placed in the center of the Helmholtz-coil apparatus. Experiments were carried out at ambient room temperature and no significant temperature change was detected between the two activated Helmholtz coils (24 ± 0.5 °C).