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The effect of pulsed electromagnetic radiation from mobile phone on the levels of monoamine neurotransmitters in four different areas of rat brain

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Abstract. – BACKGROUND: The use of mobile phones is rapidly increasing all over the world. Few studies deal with the effect of electromagnetic radiation (EMR) on monoamine neurotransmitters in the different brain areas of adult rat.

AIM: The aim of the present study was to investigate the effect of EMR on the concentrations of dopamine (DA), norepinephrine (NE) and serotonin (5-HT) in the hippocampus, hypothalamus, midbrain and medulla oblongata of adult rats.

MATERIALS AND METHODS: Adult rats were exposed daily to EMR (frequency 1800 MHz, specific absorption rate 0.843 W/kg, power density 0.02 mW/cm^2, modulated at 217 Hz) and sacrificed after 1, 2 and 4 months of daily EMR exposure as well as after stopping EMR for 1 month (after 4 months of daily EMR exposure). Monoamines were determined by high performance liquid chromatography coupled with fluorescence detection (HPLC-FD) using their native properties.

RESULTS: The exposure to EMR resulted in significant changes in DA, NE and 5-HT in the four selected areas of adult rat brain.

CONCLUSIONS: The exposure of adult rats to EMR may cause disturbances in monoamine neurotransmitters and this may underlie many of the adverse effects reported after EMR including memory, learning, and stress.

Key Words:
Electromagnetic radiation, Dopamine, Norepinephrine, Serotonin, Brain areas.

Introduction

The widespread use of mobile phones in recent years inevitably raises the question of the effect of electromagnetic fields (EMFs) emitted by such telephones on brain functions. The brain and nervous system have long been considered sensitive targets for the effects of exposure to low level radiofrequency EMFs (RF EMFs)[1]. Close-range exposure to these EMFs allows 75% of the energy generated by mobile telephone to penetrate the head reaching a depth of several centimeters[2].

Much experimental evidence of nonthermal influences of microwave radiation on living systems has been published during the last three decades. The currently available results suggest that some aspects of cognitive function and some direct measures of brain and body physiology may be affected by exposure to EMFs emitted by mobile telephones[3]. Clinical studies in humans have shown possible effects on sleeping conditions and memory function[4]. Moreover, previous reports indicate a dynamic response of the nervous system to radiofrequency radiation (RFR) depending on the duration and number of exposures, and interaction of these two parameters. In addition, different brain regions could respond differently to RFR[5].

Early studies have reported changes in various neurotransmitters (catecholamines, serotonin and acetylcoline) in the brain of animals only after exposure to high intensities of RFR[6-9]. However, there are more recent studies that show changes in neurotransmitter functions after exposure to low intensities of RFR.

Several investigators found changes in different cholinergic parameters such as acetylcholine concentration[9] and release[10], choline uptake[11,12] and acetylcholinesterase activity[13,14] after exposure to RFR. Moreover, EMR-induced alterations in both excitatory and inhibitory amino acid neurotransmitters have been reported[15-18]. Noor et al[18] suggested that the changes in amino acid concentrations may underlie the reported adverse effects of using mobile phones.

However, few studies were carried out on the effect of EMR on monoamine neurotransmitters[19-22], all of them using whole brain and short term exposure.

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Due to the shortage of the literature on the effect of EMR on monoamine neurotransmitters in different areas of rat brain, the aim of the present study was to investigate the effect of chronic EMR exposure (frequency 1800 MHz, specific absorption rate 0.843 W/kg, power density 0.02 mW/cm², modulated at 217 Hz) on dopamine (DA), norepinephrine (NE) and serotonin (5-HT) in the hippocampus, hypothalamus, midbrain and medulla oblongata of adult rats.

Materials and Methods

Experimental Animals

The experimental animals used in the present study were adult male Wistar albino rats. The animals were obtained from the animal house of the National Research Center, Egypt. They were maintained on stock diet and kept under fixed conditions of housing and handling. All experiments were carried out in accordance with the research protocols established by the Animal Care Committee of the National Research Center, Egypt which followed the recommendations of the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985).

Chemicals

Perchloric acid (Merck, Darmstadt, Germany) was used for homogenization. Norepinephrine bitartrate salt (Sigma, St: Louis, MO, USA), dopamine hydrochloride and 5-hydroxytryptamine hydrochloride (Sigma-Aldrich, St. Louis, MO, USA) were used for standard solution. Heptane sulfonic acid (PARK, Northampton, UK), HPLC-grade methanol (BDH, Chemical Ltd., Poole, Dorset, UK), analytical grade sodium acetate (Roth, Bavaria, Germany), dibutylamine, EDTA, o-phosphoric acid (Sigma-Aldrich, St. Louis, MO, USA), dibutylamine (Sigma-Aldrich, St. Louis, Mo, USA) and deionized water were used to prepare the mobile phase.

Electromagnetic Exposure

The EMR exposure system and method of exposure were described in detail by Khadrawy et al[17].

Experimental Design

Adult rats were exposed to EMR at a frequency of 1800 MHz, a power density of 0.02 mW/cm^2 and an average specific absorption rate 0.843 W/kg for 1 hour daily. A group of animals were placed at the same time in similar containers for 1 hour under the same conditions away from the RF source and served as control animals. Following exposure, the animals were returned back to their cages in the animal house. The animals were exposed to the EMR for 1 hour daily and were then sacrificed after 1 month, 2 months or 4 months of daily exposure. The rats were sacrificed one hour after the last exposure of each time segment. One subgroup from the exposed animals was left for 1 month without exposure (after 4 months of daily exposure) to study the withdrawal effect of the exposure and were then sacrificed with a group of the control animals.

Handling of Tissue Samples

Both the control and exposed rats were sacrificed by sudden decapitation. Immediately, the brain of each animal was quickly removed and dissected to hippocampus, hypothalamus, midbrain and medulla oblongata. Each brain area was then weighed and frozen (at –42° C) until analyzed.

Determination of Monoamine Concentrations

The procedure used in the present study was based on the method described by Lakshmana and Raju[23] for the simultaneous quantitative determination of NE, DA and 5-HT by high-performance liquid chromatography coupled to fluorescence detection (HPLC-FD) using their native fluorescence.

Tissue Preparation

Each brain area was homogenized by a Heidolph Diax 900 homogenizer (Germany) in 1 ml of 0.1 M perchloric acid and centrifuged at 15777 r.p.m. for 30 minutes at 4°C using a high speed cooling centrifuga (type 3k-30, Sigma, Osterade-am-Harz, Germany). The clear supernatant was filtered through a Hamilton syringe provided with a disposable syringe filter and 100 µl of each sample were finally injected into the HPLC system. NE, DA and 5-HT were detected at an excitation wavelength of 280 nm and an emission wavelength of 315 nm.

Chromatography

The HPLC system consisted of a Wellchorm Mini-star K-501 pump (Knauer, Berlin, Germany), a Knauer model D 14163-syring-loading sample injector (Germany), an Ultracarb 3u C-18 reversed phase column (150 × 4.60 mm F.d., 3

μm) from Phenomenex (Inc., Torrance, CA, USA), an interface box V7566 Version 0696 (Knauer, Germany) and a fluorescence spectrophotometer (RF-10 AxL-Shimadzu, Kyoto, Japan). The mobile phase consisted of sodium acetate (0.02 M), methanol (16%), EDTA (0.2 mM), heptane sulphonic acid (0.055%) and dibutylamine (0.01%, V/V) dissolved in deionized water and adjusted to pH 3.81 with o-phosphoric acid. The flow rate was 0.5 ml/min.

Statistical Analysis

The concentrations of the monoamines were expressed in μmole/g fresh tissue and the data were presented as mean ± SEM. Statistical comparisons between control and treated animals were carried out by the independent student's *t*-test using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) software in a PC-compatible computer. The level of significance was set at $p < 0.05$.

Results

The exposure of adult rats to EMR resulted in a significant decrease in DA concentration in the hippocampus after 2 months and after stopping exposure for 1 month. However, a significant increase in NE levels occurred after 4 months of daily exposure. In addition, a significant increase in 5-HT levels was obtained in the hippocampus of adult rats after 1 and 2 months and after 1 month of stopping exposure.

In the hypothalamus, EMR exposure induced a significant decrease in DA levels in adult rats after 2 months whereas a significant increase was recorded after 4 months. An increase in 5-HT levels was obtained after 1 and 4 months of daily EMR exposure and continued after 1 month of stopping radiation.

In the midbrain of adult rats, a significant decrease in NE levels was obtained after 2 months of daily EMR exposure. A significant decrease also occurred in DA and NE levels after stopping EMR exposure for 1 month. On the contrary, 5-HT levels increased significantly after 4 months of daily EMR exposure.

The daily exposure of adult rats to EMR resulted in a significant increase in DA levels in the medulla oblongata after 1 month and in NE and 5-HT levels after 4 months. After stopping exposure, however, a significant decrease in both DA and NE occurred.

Discussion

The present study revealed significant increases in 5-HT concentrations in the hippocampus of adult rats after 1 and 2 months of daily exposure to EMR (frequency 1800 MHz, SAR 0.843 W/kg, power density 0.02 mW/cm², modulated at 217 Hz). This significant increase reappeared after stopping EMR exposure for 1 month. There were significant decreases in DA content in the hippocampus after 2 months of daily EMR exposure and after stopping EMR for 1 month.

Studies have shown that the hippocampus is an important region for the acquisition and consolidation of explicit forms of declarative memories[24]. The CA1 region of the hippocampus is rich in 5-HT receptors[25] and 5-HT containing terminals[26] originating from the brain stem neurons located in the raphe nuclei[27]. Several studies provided evidence that 5-HT exerts an inhibitory influence on learning and memory and has a negative effect on one or more of hippocampal pathways involved in spatial information processing[28,29]. Meeter et al[30] found that a low level of 5-HT in the hippocampus may constitute a permissive criterion for storage and retrieval, a higher level of 5-HT in the hippocampus a stricter criterion.

On the contrary, dopamine can promote long-term potentiation, a widely accepted model of hippocampus-dependent memory[31], and improve hippocampus-dependent learning in animals[32].

It could be concluded that the increase in serotonin and decrease in dopamine in the hippocampus after daily EMR exposure of adult rats may affect memory and learning ability in these animals. The relapse of these changes in serotonin and dopamine after stopping exposure to EMR may indicate the persistence of some changes in monoamines in the hippocampus of adult rats, at least after 1 month of stopping EMR.

In support of the present conclusion, it has been reported that rats exposed to pulsed EMR showed retarded learning and a deficit in spatial "reference" memory[33]. Alterations of memory functions were also evidenced by Nittby et al[34] after long-term exposure of rats to GSM-900 microwaves and were later confirmed by Fragopoulou et al[35] and Narayanan et al[36] in mice and rats, respectively. Hyland[37] reported that memory impairment is consistent with the finding that microwave radiation targets the hippocampus.

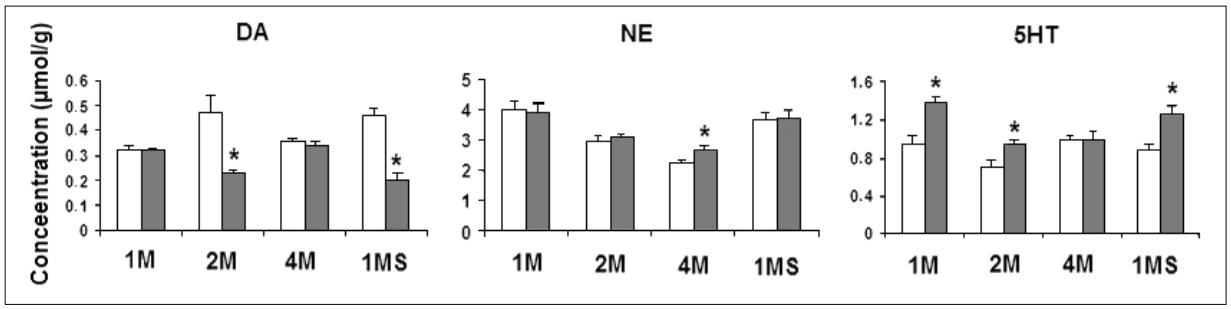

Figure 1. The effect of electromagnetic radiation on monoamine concentrations in the hippocampus of adult rats. DA: dopamine; NE: norepinephrine; 5HT: serotonin; M: month: MS: month of stopping.

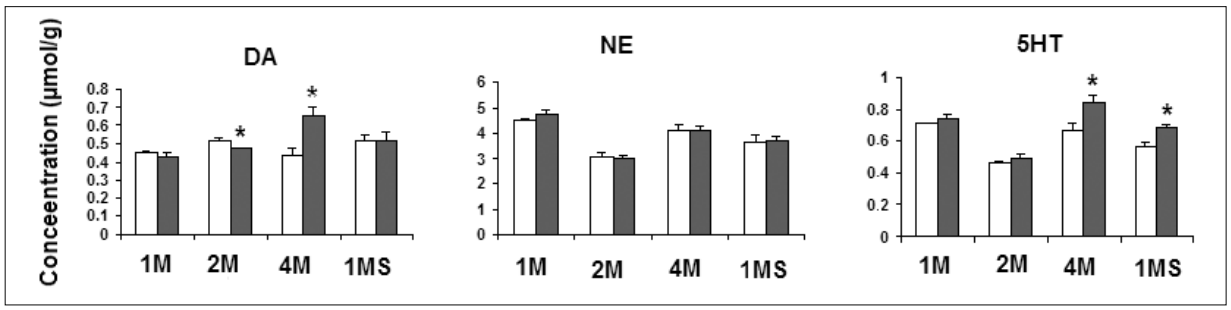

Figure 2. The effect of electromagnetic radiation on monoamine concentrations in the hypothalamus of adult rats. DA: dopamine; NE: norepinephrine; 5HT: serotonin; M: month: MS: month of stopping.

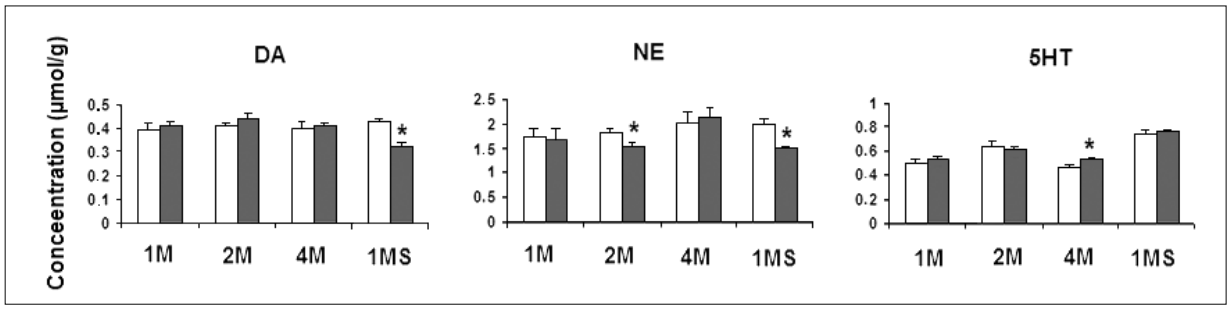

Figure 3. The effect of electromagnetic radiation on monoamine concentrations in the midbrain of adult rats. DA: dopamine; NE: norepinephrine; 5HT: serotonin; M: month: MS: month of stopping.

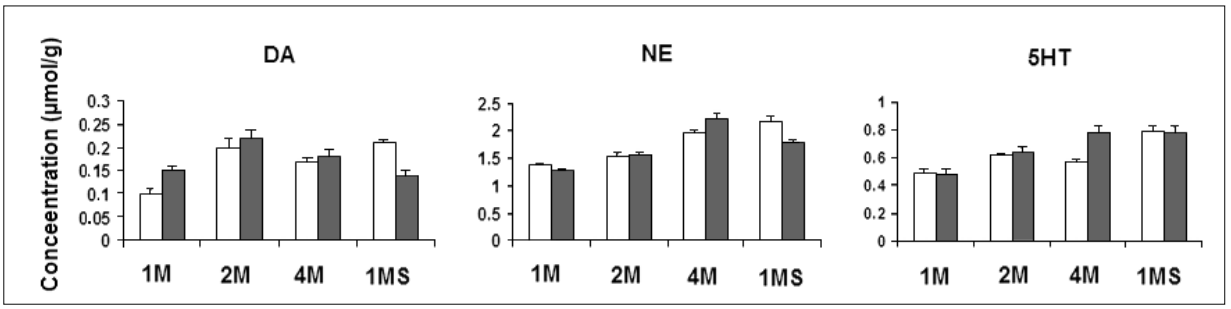

Figure 4. The effect of electromagnetic radiation on monoamine concentrations in the medulla of adult rats. DA: dopamine; NE: norepinephrine; 5HT: serotonin; M: month: MS: month of stopping.

The delayed significant increase in hippocampal NE in adult animals after 4 months of daily exposure may represent an attempt of the brain to overcome the disturbance in some hippocampal functions induced by the increase in 5-HT and decrease in DA under the effect of EMR. The return of 5-HT content after 4 months to a control like level may support this suggestion in view of the negative correlation between serotonin and norepinephrine.

Consistent with the previous suggestion, Schroeter et al[38] showed that the hippocampus has one of the densest inputs of adrenergic terminals in the CNS. Gertner and Thomas[24] found a critical role for NE in the acquisition of working memory using a more standard protocol of the radial arm maze in mice.

The locus ceruleus (LC) is the primary source of forebrain NE and is known to be involved in attention and memory[39]. It has been reported that one target of LC projections is the hippocampus, a structure implicated in memory[40].

The present study revealed a significant increase in medullary NE in adult rats after 4 months of daily EMR exposure. However, after stopping EMR for 1 month, there was a significant decrease in medullary NE. From these reports and the present data, it may be suggested that the increase in medullary NE may represent a source of its supply to the hippocampus in support of the attempt of the brain to relieve the attention and memory deficits caused by EMR through the pathway from LC to the hippocampus. However, this supply was exhausted after 1 month of stopping EMR as medullary NE decreased.

Lisman and Grace[32] developed the concept that the hippocampus and the midbrain dopaminergic neurons of the ventral tegmental area (VTA) form a functional loop which regulates the entry of information into long-term memory. The hippocampus receives dopaminergic input[41], which comes from both the substantia nigra and the VTA.

In the present study, EMR exposure of adult rats resulted in a highly significant decrease in midbrain DA content after stopping EMR exposure for 1 month. This may reduce the dopaminergic input to the hippocampus of adult rats and thus assist in the adverse effects of DA depletion in this area. It may be proposed that this decrease in midbrain DA may affect arousal in rats and participate in the reduced learning and memory abilities reported after EMR exposure. In line with the present postulation, Noor et al[18] reported disturbances in amino acid neurotransmitters in the midbrain of young rats and suggested that the young users of mobile phones may be under the risk of impaired alertness.

Our findings showed increases in hypothalamic 5-HT content of adult rats after 4 months of EMR exposure and after stopping EMR exposure for 1 month. It may be proposed that these increases may cause stress in the hypothalamus of adult rat during and after stopping exposure and suggests that persistent changes occur in the nervous system after stopping EMR exposure at least for 1 month, particularly in 5-HT pathways. It could be concluded that hypothalamic 5-HT is more sensitive to EMR exposure than NE since NE showed minor changes after EMR exposure.

Consistent with the above suggestion, it has been reported that serotonergic mechanisms exert an excitatory influence on the entire hypothalamic-pituitary-adrenal (HPA) axis[42]. It has been found that local application of serotonin into the hypothalamus produced a dose dependent increase in corticotrophin releasing hormone (CRH) release[43] and adrenocorticotropic hormone (ACTH) release directly from the pituitary[44].

Moreover, various lines of evidence suggest that responses of the central nervous system to RFR could be a stress response[45]. The Authors found that RFR activated the stress hormone, CRH. Inaba et al[46] found that plasma levels of ACTH increased significantly after microwave exposure in rats. Moreover, Mann et al[47] reported that EMFs at a frequency of 900 MHz pulsed with 217 Hz resulted in an alteration in the hypothalmo-pituitary-adrenal axis activity with a slight transient elevation in serum cortisol level immediately after onset of field exposure. Imaida et al[48] observed that corticosterone and ACTH levels in serum were significantly increased after exposure of rats to 1.439 GHz.

Stress may have a detrimental effect on the hippocampus[49]. The hippocampus is a target of stress hormones, and an especially plastic and vulnerable region of the brain[50]. The elevation of circulating corticosterone concentrations exerts an inhibitory influence on learning and memory retrieval[51].

Conclusions

The exposure to pulsed EMR emitted from mobile phone (frequency 1800 MHz, SAR 0.843 W/kg, power density 0.02 mW/cm^2, modulated at 217 Hz) affects brain functions through the

changes in monoamines neurotransmitters, the most affected areas being the hippocampus and hypothalamus which are two important components of the limbic system. This is consistent with the report of Dindi et al[3] that subcortical regions may contain the most sensitive structures to EMF influence.

Thus, it may be recommended that the use of mobile phone should be kept within necessary limits in order to protect or reduce the undesired neurological effects of EMR exposure.

Conflict of Interest

None.

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