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Impairment of long-term potentiation induction is essential for the disruption of spatial memory after microwave exposure

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Abstract

Purpose: **To assess the impact of microwave exposure on learning and memory and to explore the underlying mechanisms.**

Materials and methods**: 100 Wistar rats were exposed to a 2.856 GHz pulsed microwave field at average power densities of 0 mW/cm^2, 5 mW/cm^2, 10 mW/cm^2 and 50 mW/cm^2 for 6 min. The spatial memory was assessed by the Morris Water Maze (MWM) task. An in vivo study was conducted soon after microwave exposure to evaluate the changes of population spike (PS) amplitudes of long-term potentiation (LTP) in the medial perforant path (MPP)-dentate gyrus (DG) pathway. The structure of the hippocampus was observed by the light microscopy and the transmission electron microscopy (TEM) at 7 d after microwave exposure.**

Results: **Our results showed that the rats exposed in 10 mW/cm^2 and 50 mW/cm^2 microwave displayed significant deficits in spatial learning and memory at 6 h, 1 d and 3 d after exposure. Decreased PS amplitudes were also found after 10 mW/cm^2 and 50 mW/cm^2 microwave exposure. In addition, varying degrees of degeneration of hippocampal neurons, decreased synaptic vesicles and blurred synaptic clefts were observed in the rats exposed in 10 mW/cm^2 and 50 mW/cm^2 microwave. Compared with the sham group, the rats exposed in 5 mW/cm^2 microwave showed no difference in the above experiments.**

Conclusions: **This study suggested that impairment of LTP induction and the damages of hippocampal structure, especially changes of synapses, might contribute to cognitive impairment after microwave exposure.**

Keywords: Microwave, synaptic plasticity, long-term potentiation (LTP), hippocampus, rats

Introduction

Microwaves, as electromagnetic waves ranging in frequency from 300 MHz to 300 GHz, are widely used in communications, medical treatments, military affairs and industry. Over the past decade, there has been a growing concern on the potential health hazards caused by exposure to microwaves. The central nervous system (CNS) is believed to be vulnerable to microwave radiation, which will result in memory loss (Orendacova et al. 2007, Campisi et al. 2010, Li et al. 2012). However, the mechanisms of microwave-induced memory loss and learning disabilities remain unknown.

The Morris Water Maze (MWM) test, a behavioral procedure widely used in behavioral neuroscience to test spatial memory in rodents, has been proven to be strongly correlated with hippocampus-related cognitive function and N-methyl-D-aspartic acid (NMDA) receptors' function (Morris 1984). This classic method has been frequently used to test the spatial learning and memory after microwave radiation. However, because of the differences of the parameters of microwave exposure setups, the performance of animals in the behavioral tests varied (Wang and Lai 2000, Dubreuil et al. 2002, Kumlin et al. 2007). Therefore, the results of MWM about microwave radiation among different scholars had poor comparability.

Long-term potentiation (LTP), one of the best studied but still intriguing phenomena of synaptic plasticity, is believed to be one of the most important cellular mechanisms for learning and memory (Jensen and Overgaard 2011). LTP in the medial perforant path (MPP)-dentate gyrus (DG) pathway, as the first identified pathway, has been proved to be NMDA-dependent and has become the dominant model of activity-dependent synaptic plasticity in the mammalian brain (Malenka 2003). However, few studies have been conducted on LTP in the MPP-DG pathway after microwave exposure.

The hippocampus plays an important role in processing and remembering spatial information (Bahar and Shapiro 2012). Its normal structure is essential for carrying out its functions. Therefore, to determine the impact of microwave

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on CNS, the histopathological analysis is an indispensable approach to evaluate the injury of hippocampus structure and function in rats.

To gain insights into the effect of microwave exposure on the animal brain and the underlying mechanism, we used an appropriate animal model, the MWM task, LTP recordings in the MPP-DG pathway and the hippocampus structure observation to find out more about the effect of microwave exposure on CNS.

Materials and methods

Animals

100 male Wistar rats (225 ± 25 g, 8 weeks) were purchased from the experimental animal center (Beijing, China) and maintained in specific pathogen-free (SPF) grade animal facility. All experiments were performed between 08:00 and 15:00 h. All protocols were approved by the Institutional Animal Care and Use Committee. To eliminate the difference of body weight, the rats were divided into four groups by the stratified random method: the sham group, the 5 mW/cm^2 group, the 10 mW/cm^2 group and the 50 mW/cm^2 group (Table I). Rats in the three exposure groups were exposed with 2.856 GHz radiation source for 6 min. To eliminate other types of psychophysiological effects, the rats in the sham group were also handled and processed parallel to those in the exposure groups, except for microwave radiation.

Microwave exposure system

The microwave source, a klystron amplifier model JD 2000 (Vacuum Electronics Research Institute, Beijing, China), was capable of generating pulsed microwaves at S-band with the frequency of 2.856 GHz. Microwave energy was transmitted by rectangular waveguide and A16-dB standard-gain horn antenna to an electromagnetic shield chamber ($7 \times 6.5 \times 4$ m). The diagonal of the antenna was 33 cm. The interior walls of the chamber were covered with 500 mm and 300 mm pyramidal microwave absorbers to minimize reflections (>45 dB). The emitted power was measured with a semiconductor detector connected to a directional coupler at one port of a circulator and displayed on an oscilloscope. The distance from the antenna to the top of the animal cage was 1.4 m. The rat container, with 20 houses to reside in each batch, was made of Plexiglas. The dimension of each house could be adjusted and made in such a way that the rats were comfortably placed (Figure 1).

The average power densities were measured using a waveguide antenna, the GX12M1CHP power meter (Guanghua Microelectronics Instruments, Hefei, China) and GX12M30A power heads. The microwave pulses were delivered at 200 pps, 200 pps and 500 pps, respectively, with a pulse width of 500 ns. The peak field power densities tested with a calibrated detector and an oscilloscope for the three exposure groups were 50, 100, and 200 W/cm^2, respectively. The average field power densities were calculated to be 5, 10, 50 mW/cm^2. The output power of the radiation source for the three exposure groups was 0.35, 0.7 and 1.4 MW.

Table I. The number of rats in different groups for each part of the experiment.

Experimental methods	Groups			
	Sham group	5 mW/cm^2	10 mW/cm^2	50 mW/cm^2
MWM	15	15	15	15
LTP recordings	5	5	5	5
H&E & TEM	5	5	5	5

MWM, Morris Water Maze; LTP, long-term potentiation; H&E, Hematoxylin and eosin; TEM, transmission electron microscopy.

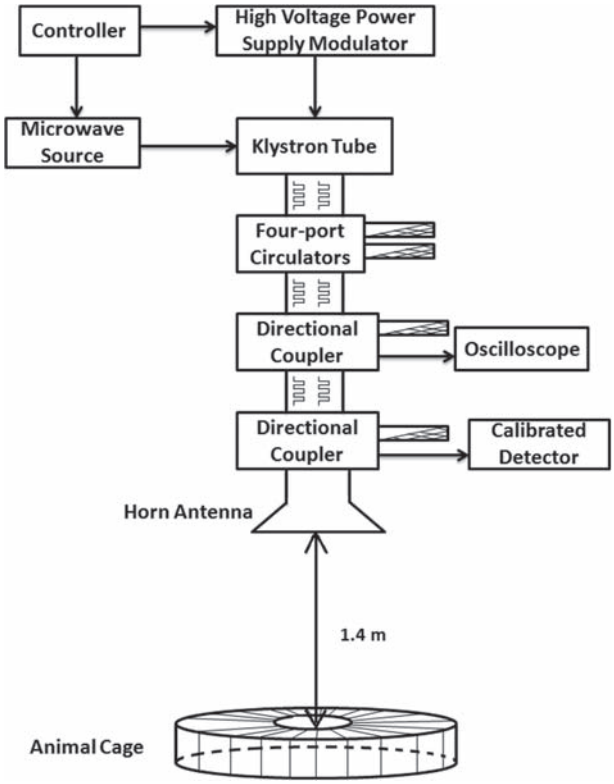

Figure 1. Schematic diagram of experimental set-up for microwave exposure.

Dosimetry

The rats in different boxes of the container were oriented at different positions. Regarding the different polarization and the heterogeneous distribution of the field power densities (FDP), the special absorption rate (SAR) of each rat had to be calculated separately under plane wave exposure. In order to minimize the error of SAR, we calculated the SAR in different locations of the container and provided the final value in terms of the average form.

The SAR calculation was based on the finite difference time domain (FDTD) method and the formula: $SAR = \sigma E^2/\rho$ (W/kg) (Esmekaya et al. 2010). In the formula, E is the electric field strength (V/m), σ (sigma) is the electric conductivity (S/m), and ρ (rho) refers to the sample density (kg/m^3). In our study, the software for calculating SAR in our study was the simulation platform Empire: IMST-Empire v-4.10 (GmbH, Kamp-Lintfort, Germany). The rat model for calculating SAR, constructed from magnetic resonance imaging (MRI) sections, was a 370 g male Sprague-Dawley rat with 36 different tissues. The original resolution of the model was $0.39 \times 0.39 \times 1$ mm resulted in approximately 6.6 million voxels to make up a three-dimensional array. The cubes

possessed a tag to identify the tissue type. Under this condition, we normalized the model to have a mass of 230 kg with the voxel size of $0.33 \times 0.33 \times 0.85$ mm, the average mass of rats used in our experiment and calculated the average SAR for brain. Therefore, the SAR of brain per unit power density (1 mW/cm^2) was 0.70 ± 0.05 (W/kg). Accordingly, the average SAR of brain were calculated to be 3.5, 7 and 35 W/kg for the 5, 10 and 50 mW/cm^2 groups. The uncertainty of SAR values was less than 2 dB due to uncertainty of the field value, amplifier drifts, and variations of location, orientation, posture and anatomy. A series of measurements in rat cadavers were also verified the reliability of the theoretical calculations.

Body temperature measurement

The temperature of the hippocampus and rectum was simultaneously measured by an optic fiber thermometer m3300 (Luxtron Corp., Santa Clara, CA, USA). Two Teflon catheters were inserted into the brain and rectum. The optic fiber probe was then inserted into the catheter and located at the tips of the catheter. Temperature signals were recorded at a 1.0-Hz sampling rate.

The MWM behavioral task

The experiment was carried out in a circular pool (150 cm in diameter) filled with water maintained at $23°C \pm 0.5°C$ in a room with constant brightness. The pool was divided into four equal quadrants. In the target quadrant, a platform (12×15 cm) was submerged 1.5 cm below the water surface. The navigation test and spatial exploration test were digitally recorded by the SLY-MWM system (Beijing Sunny Instrument Co. Ltd, Beijing, China).

Sixty rats ($n = 15$ per group) were trained to find the submerged platform (four trials for each session). Each trial had a maximum duration of 60 sec. In the training tests, the rats that did not find the platform within 60 sec were placed on the platform for 20 sec. Navigation tests were performed at 6 h, 1 d and 2 d after microwave radiation. If the rat was unable to find the platform, its escape latency would be recorded as 60 sec. At 3 d after microwave exposure, the platform was removed. The animals were tested for the number of crossings of the area marking the exact position of the former platform in 60 sec.

The LTP recordings in MPP-DG pathway

Shortly after microwave exposure, 20 rats ($n = 5$ per group) were anesthetized with an intraperitoneal (IP) injection of urethane (1.2 g/kg) (Sinopharm Chemical Reagent Beijing Co., Beijing, China) and fixed in a stereotaxic head holder (Stoelting Co., Wood Dale, IL, USA) for LTP induction. Holes were made in the skull by a dental drill (Saeshin Precision Ind. Co., Daegu, Korea). The electrodes, thin stainless-steel needles (0.25 mm diameter), were coated with epoxy resin except for the tip. The stimulating electrodes were placed on the MPP [+7.9 anteroposterior (AP), ±4.2 mediolateral (ML) mm from bregma] and the recording electrodes were inserted into the dentate molecular layer (+3.8 AP, ±2.0 ML mm from bregma) to induce PS. The final position of the stimulating and recording electrodes was adjusted to produce maximum responses.

Single-pulse test stimuli were applied to the MPP at an interval of 30 sec. The stimulus intensity was adjusted to produce PS with a slope that was approximately 50% of the maximum amplitude. After a 30-min base line recording, the high-frequency stimulation (HFS) was delivered to the perforant pathway with test stimulus intensity. The HFS comprised three trains of 20 stimuli with an interstimulus interval of 5 ms (200 HZ) and an intertrain interval of 30 sec. Recordings were analyzed with pClamp 10 (MDC, CA, USA).

Hematoxylin and eosin (H&E) staining and transmission electron microscopy (TEM) observation

At 7 d after microwave exposure, 20 rats ($n = 5$ per group) were anesthetized with sodium pentobarbital (50 mg/kg, IP) (Sinopharm Chemical Reagent Beijing Co. Ltd, Beijing, China).

The left parts of the brain were dissected out and fixed in 10% buffered formalin solution for H&E staining. Five coronal brain sections (5 μm), including the hippocampus, were prepared. The sections were dipped in hematoxylin (Sinopharm Chemical Reagent Beijing Co. Ltd, Beijing, China) for 3 min, washed in tap water for 30 min, and destained in warm water for several seconds. The sections were washed again in running water for 15 min, dipped in eosin (Sinopharm Chemical Reagent Beijing Co. Ltd, Beijing, China) for 15 sec prior to washing again for 20 min, and then dehydrated in an alcohol gradient, followed by xylene clearance and coverslipping. The stained sections were observed under a light microscope.

The right parts of the brain were prepared for hippocampus separation. The hippocampus samples of 1 mm^3 cube were dissected from the DG area at 7 d after microwave exposure. After being fixed in 2.5% glutaraldehyde (Merck, Darmstadt, Germany), the specimens were sequentially processed with 1% osmium tetroxide (AppliChem, Gatersleben, Germany) graded ethyl alcohol and embedded in EPON618 (TAAB Laboratories Equipment, Berks, UK). The thin sections on copper meshes were stained with uranyl acetate and lead citrate (Advanced Technology & Industrial Co. Ltd, Hong Kong, China) for contrast. After being dried, the grids were then viewed on a TEM (H-7650, Tokyo, Japan).

Statistical analysis

To compare the escape latency and PS amplitudes, one-repeated analysis of two-way ANOVA was applied by the software of SAS 9.2. To compare the number of crossings, the data were analyzed by one-way ANOVA. Multiple comparisons were performed by the SNK analysis. Differences at $p < 0.05$ were considered to be significant.

Results

Body temperature

We simultaneously recorded the brain and rectal temperatures for 12 min. The results showed that exposure to 5 and 10 mW/cm^2 microwave did not increase the body temperature (Figure 2B, 2C). Significant changes of the brain and rectal

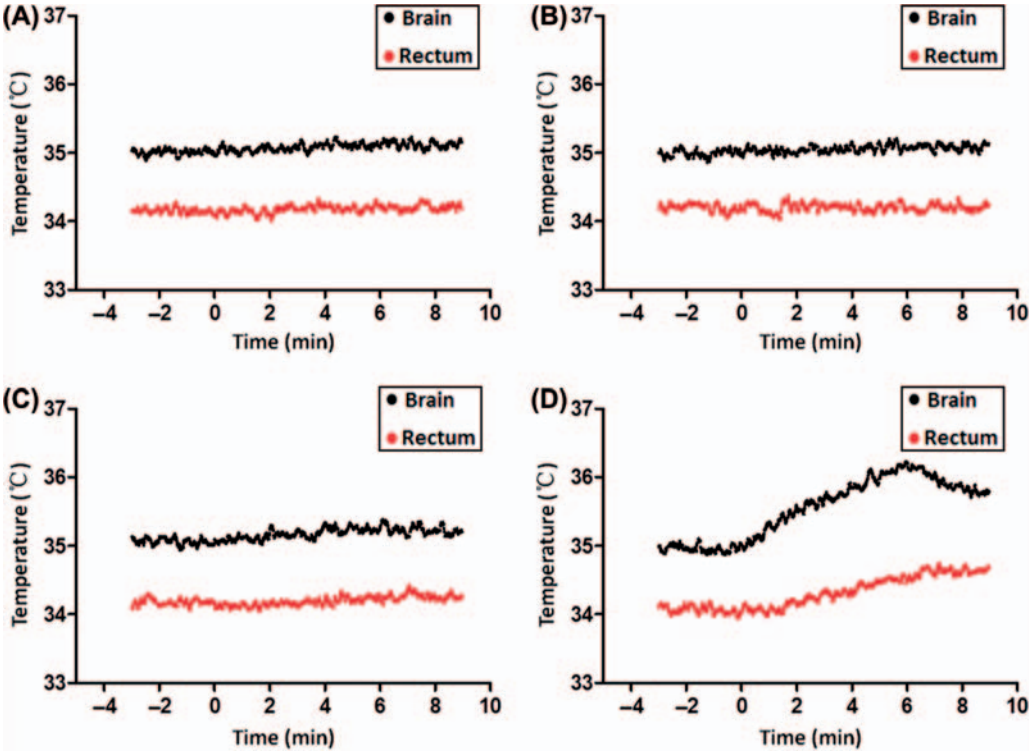

Figure 2. Brain and rectal temperature of rats among four groups. We recorded the temperatures for 12 min, including 3 min before microwave exposure, 6-min exposure time and 3 min after exposure. (A) refers to the sham group, (B) refers to the 5 mW/cm^2 group, (C) refers to the 10 mW/cm^2 group, and (D) refers to the 50 mW/cm^2 group.

temperatures were observed in 50 mW/cm^2 group after 6-min microwave exposure. The peak rise of the head temperature was calculated to be 1.2°C, compared to 0.6°C of the rectal temperature (Figure 2D).

Spatial learning and memory

The MWM tests revealed that the rats in the 10 mW/cm^2 and 50 mW/cm^2 groups developed significant prolongations in escape latency at 6 h, 1 d after microwave exposure ($p < 0.05$) (Figure 3A). The number of crossings in the 10 mW/cm^2 and 50 mW/cm^2 groups showed a significant decrease at 3 d after microwave radiation ($p < 0.05$) (Figure 3B).

LTP recorded in MPP-DG synapses

In this study, we found that rats in the 10 mW/cm^2 and 50 mW/cm^2 groups showed a significant decline in PS amplitude during 6 h after microwave exposure ($p < 0.01$) (Figure 4). There were no significant changes in the 5 mW/cm^2 group. These results showed that LTP in MPP-DG synapses was inhibited in the 10 mW/cm^2 and 50 mW/cm^2 groups.

Hippocampus structure

In the sham and 5 mW/cm^2 groups, normal neuron structures were detected by microscopy (Figure 5A, 5B). In the 10 mW/cm^2 and 50 mW/cm^2 groups, however, hippocampus neurons were significantly irregularly arranged, karyopyknosis occurred in most neurons and the nuclei shrinked into blue pieces (Figure 5C, 5D). Injury occurred in the CA3 and DG area at 7 d after microwave exposure.

Compared with the sham group (Figure 6A), the amount of synaptic vesicles in the 10 mW/cm^2 and 50 mW/cm^2 groups was decreased, and the synaptic cleft was widened or blurred (Figure 6C, 6D). Meanwhile, swollen mitochondria were observed in the 10 mW/cm^2 and 50 mW/cm^2 groups along with the cristae disorders and reduction in number (Figure 6C, 6D). There were no differences between the 5 mW/cm^2 group (Figure 6B) and the sham group.

Discussion

The most distinctive feature of CNS is its astonishing ability to adapt to the environment and to improve its performance over time and experience (Benfenati 2007). Due to differences in exposure devices and radiation parameters, such as frequency, power density and exposure time, the previous studies about microwave exposure on CNS were incomparable. Moreover, the mechanisms underlying hazardous health effects of microwave radiation on learning and memory were not clear.

Many studies have confirmed that microwave radiation can cause impairment to learning and memory and changes of synaptic plasticity (Li et al. 2008, Nittby et al. 2008, Sinha 2008, Narayanan et al. 2009, Vorobyov et al. 2010), whereas others have proved otherwise (Cosquer et al. 2005, Kumlin et al. 2007, Ammari et al. 2008, Eltiti et al. 2009). These previous studies mainly focused on the 2.45 GHz, 900 MHz and 1800 MHz microwaves. Little research was conducted on the 2.856 GHz pulsed microwave with higher SAR (over 5 W/kg). In the present study, the classic MWM test was used

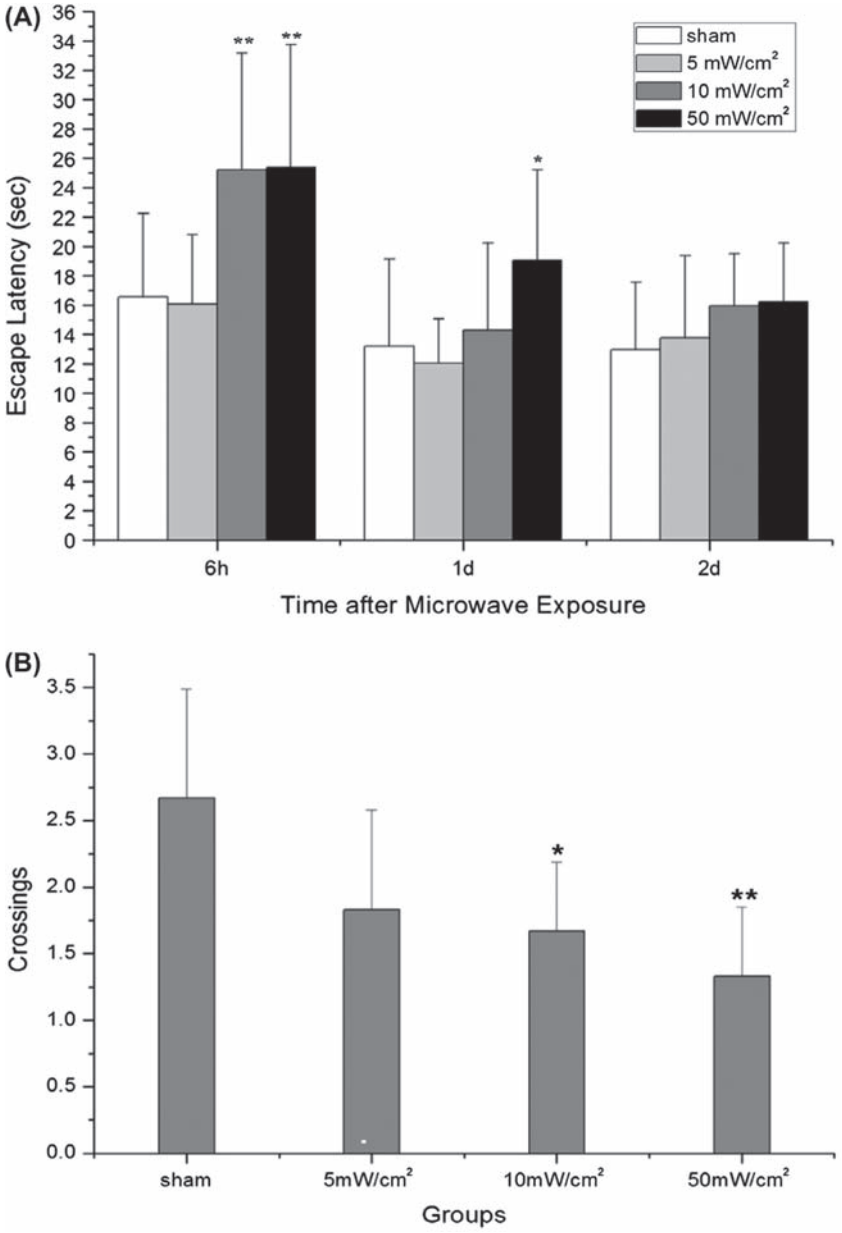

Figure 3. Cognitive tests of rats in the Morris water maze among four groups. (A) Escape latencies during 6 h–2 d after microwave exposure in the navigation test. (B) The number of crossings in the probe test at 3 d after microwave exposure. Data are represented as mean (+ standard error) and compared $^{*}p < 0.05$, $^{**}p < 0.01$ to respective sham group.

to evaluate the effects of microwave radiation on rats' cognitive functions. We found both in the navigation tests and in the probe test, the performance of rats in the 10 mW/cm^2 and 50 mW/cm^2 groups was worse than that in the sham group.

LTP, an experimental form of synaptic plasticity that results in a long-lasting increase in the strength of synaptic transmission, is one of the main cellular mechanisms of learning and memory (Welberg 2008, Rebola et al. 2010). One of the first descriptions of LTP outside the hippocampus concerned the hippocampal input to the prelimbic cortex in vivo (Doyere et al. 1993, Lynch 2004). The importance of LTP in MPP-DG synapses has long been recognized (Laroche et al. 1990, Squire 1992, Lavenex and Amaral 2000). In our study, we found that microwave exposure ($\geq$ 10 mW/cm^2) could affect the synaptic activity and destroy the induction of LTP. The findings might help us understand the bad performance of rats in the 10 mW/cm^2 and 50 mW/cm^2 groups in the MWM test. However, these results are contradicted with the findings of Pakhomov et al. (2003) and Jadidi et al. (2007), probably due to the different LTP recording methods and exposure conditions. Moreover, according to Figure 4, the curve of the 50 mW/cm^2 group was closer to that of the sham group than to that of the 10 mW/cm^2 group, indicating no significant dose-effect relationship. The fact is that amplitude of PS alone does not reflect the ability of the entire learning and memory. It has to be combined with other parameters to reflect the spatial memory, such as, the results of MWM. In our experiment, we found significantly decreased PS amplitudes at the 10 mW/cm^2 and 50 mW/cm^2 groups compared with the sham group, which is consistent with results of MWM and hippocampus structure observation.

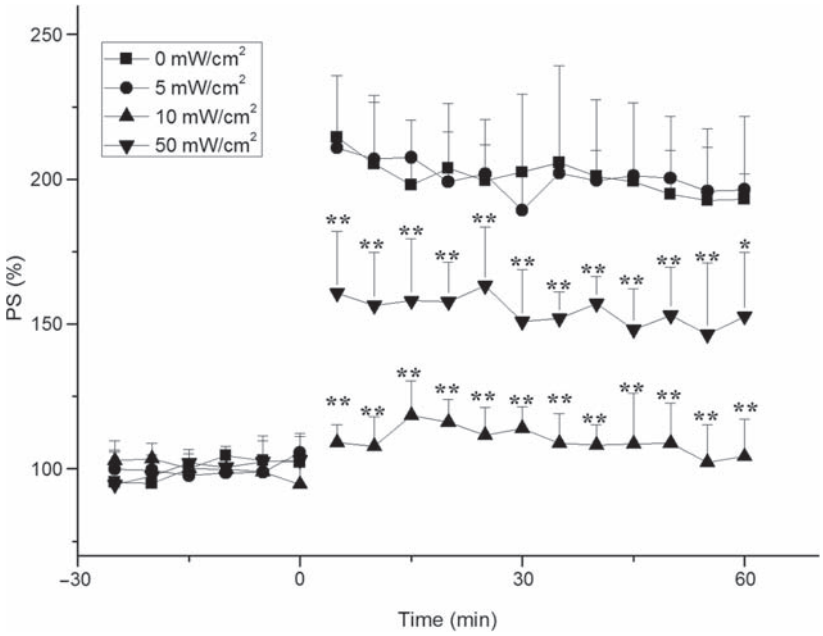

Figure 4. PS amplitudes of rats in four groups. Rats were immediately subjected to record PS after microwave exposure. All experiments were completed within 6 hours. Data are represented as mean (+ standard error) and compared $^{*}p < 0.05$, $^{**}p < 0.01$ to respective sham group.

The issue of thermal and non-thermal effects is also a factor in an ongoing debate about possible health risks of microwave energy (Foster 2000, Foster and Glaser 2007). Non-thermal effects occur when the emitted energy of the radiofrequency field does not significantly increase the temperature of a cell, tissue or an organism, but instead causes some physical or biochemical changes. There are some hypotheses on how non-ionizing radiation, which involves microwave, visible light, infrared and other electromagnetic forms of radiation, can affect organisms at a non-thermal level. One is that microwave radiation can change cell membrane signal transduction such as Na^{+}, K^{+} and Ca^{2+}. Another is concerned with the formation of free radicals. A third one is the Fröhlich's hypothesis that large

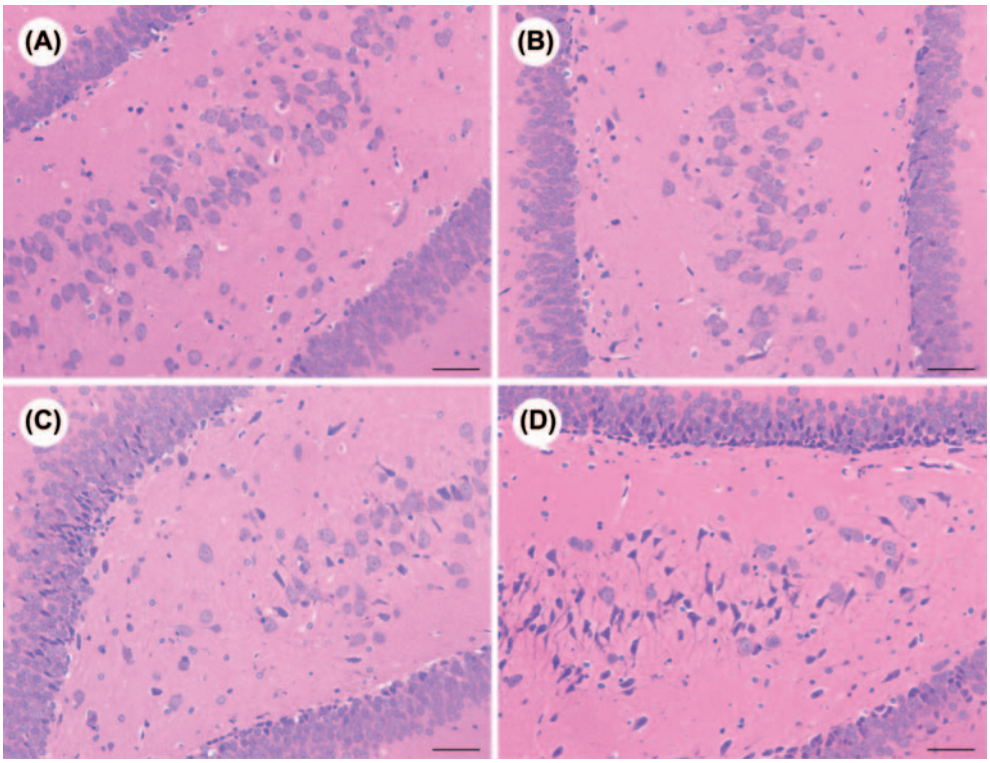

Figure 5. The effects of microwave exposure on the hippocampal structure in rats. (A) and (B) were taken respectively from the sham and 5 mW/cm^2 groups, showing basically normal neurons. (C) and (D) were taken from the 10 mW/cm^2 and 50 mW/cm^2 groups with significant necrosis of pyramidal neurons. The hippocampus was photographed at a 200× magnification. Bars = 50 μm. This Figure is reproduced in color in the online version of *International Journal of Radiation Biology*.

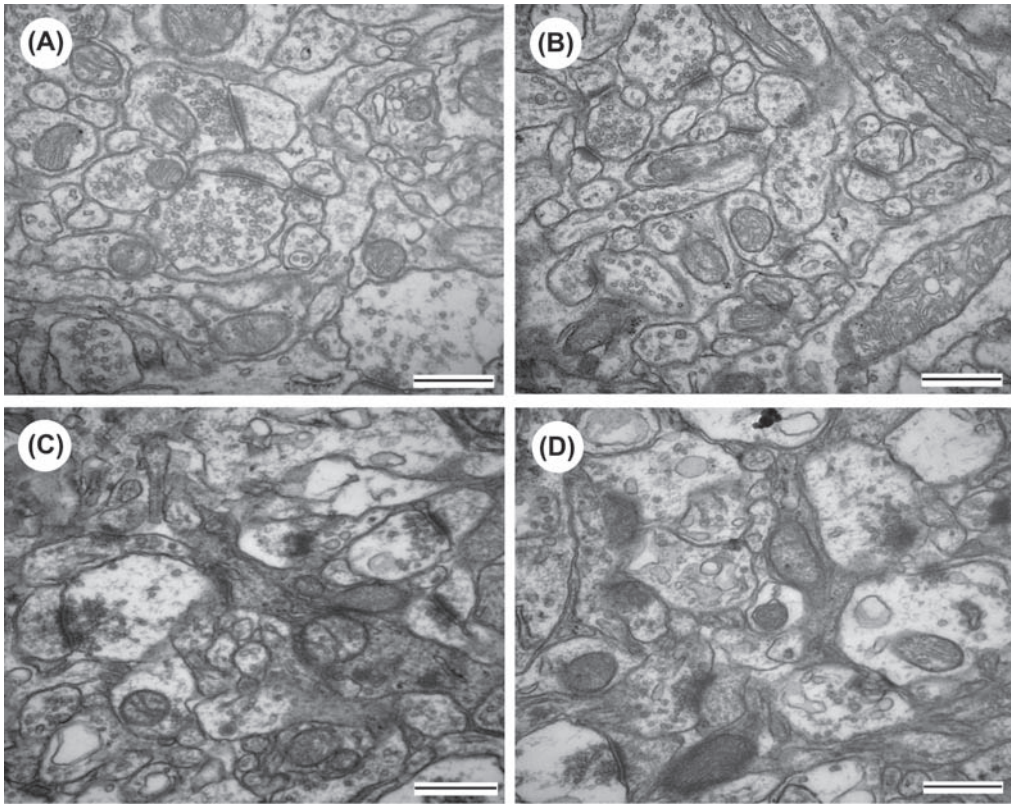

Figure 6. The ultrastructure of rat hippocampus among four groups at 7 d after microwave exposure. (A) Normal synapses with plenty of mitochondria and synaptic vesicles, clear synaptic clefts were presented in sham rats. (B) 5 mW/cm^2 group: basically normal synapses. (C–D) 10 mW/cm^2 and 50 mW/cm^2 groups: Synapses with fewer vesicles and blurred clefts. Bars = 500 nm.

molecules in the biological tissue could vibrate at frequencies that allow for absorption of external energy (Trosic et al. 2012). In our study, there were no significant increases of the head temperatures in the 10 mW/cm^2 group during the microwave exposure. However, changes of MWM, LTP and historical observations were found in this group, which may indicate that the non-thermal effects are dominant. Meanwhile, in 50 mW/cm^2 group, the peak rise of head temperature was 1.2°C. Results of the behavioral test, LTP recording and historical observations showed that significant injuries had occurred. This was possibly due to both the thermal and non-thermal effects, as the rise of temperature may trigger some stress responses. When the thermal and non-thermal effects are present simultaneously, the final effects on CNS are enhanced or diminished needs to be further explored.

LTP induction is produced as an event in postsynaptic neurons. The mechanism was found to involve a signal transduction cascade that includes release of glutamate from the synaptic vesicles, activation of the NMDA glutamate receptors at the postsynaptic membranes, Ca^{2+} entry, and activations of Ca^{2+}/calmodulin-dependent protein kinases (CaM kinases) II and IV and mitogen-activated protein kinase (MAPK). Furthermore, activation of CaM kinase IV and MAPK increased phosphorylation of cyclic AMP response element binding protein (CREB) and expression of c-Fos by stimulation of gene expression (Miyamoto 2006). In our study, decreased synaptic vesicles in the 10 mW/cm^2 and 50 mW/cm^2 groups were observed, which might serve as a clue to the impairment of LTP induction. Other variations of the hippocampal structure occurred in DG and CA3 area in the 10 mW/cm^2 and 50 mW/cm^2 groups, which was consistent with the MWM test and LTP recordings.

Therefore, we conclude that microwave exposure can impair cognitive functions by altering synaptic transmission and LTP induction. Our data may contribute to further understanding of the mechanism of neurobehavioral impairments following microwave exposure and related prevention measures.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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