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Research report

Whole body exposure to 2.4 GHz WIFI signals: Effects on cognitive impairment in adult triple transgenic mouse models of Alzheimer's disease (3xTg-AD)

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HIGHLIGHTS

- Transgenic mice becomes less anxious: reduction of latency time.
- Not affected the locomotor activity.
- Correction of the spatial memory.

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ABSTRACT

The present investigation aimed at evaluating the effects of long-term exposure to WIFI type radiofrequency (RF) signals (2.40 GHz), two hours per day during one month at a Specific Absorption Rate (SAR) of 1.60 W/kg. The effects of RF exposure were studied on wildtype mice and triple transgenic mice (3xTg-AD) destined to develop Alzheimer's-like cognitive impairment. Mice were divided into four groups: two sham groups (WT, TG; $n = 7$) and two exposed groups (WTS, TGS; $n = 7$). The cognitive interference task used in this study was designed from an analogous human cognitive interference task including the Flex field activity system test, the two-compartment box test and the Barnes maze test. Our data demonstrate for the first time that RF improves cognitive behavior of 3xTg-AD mice. We conclude that RF exposure may represent an effective memory-enhancing approach in Alzheimer's disease.

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1. Introduction

Living organisms are continuously in interaction with static magnetic field (SMFs) or electromagnetic fields (EMF). These magnetic fields can induce several bioeffects [1–7]. However, there have been few studies reporting biological and behavioral data under SMFs. Moreover, radiofrequency (RF) was shown to affect cognitive functions in both humans [8,9] and animals [10]. Such alteration might be effective against spatial learning and memory loss [11], but the evidence for this remains equivocal. Sienkiewicz and colleagues [12] reported that low intensity RF fields at 700 MHz can alter electrical activity in hippocampal slices from rat brain. Similarly, a study by Xu et al. [13] showed that exposure to 1800 MHz mobile phone (GSM) frequency signals (15 min per day for 8 days, specific absorption rate (SAR) of 2.40 W/kg) reduces excitatory synaptic activity in cultured hippocampal neurons. Interestingly, the hippocampus is involved in spatial learning and memory processes in rodents [14,15]. Exposure to RF is believed to induce performance deficit in rodents in a spatial memory task [16].

However, other studies reported that whole-body exposure to high frequency (2450 MHz) EMFs did not induce any memory deficit in rats tested in the 12-arm radial maze [17,18]. Similarly, Dubreuil et al. [16,19] did not find any effect on spatial memory in rats subjected to head-only exposure to 900 MHz GSM signals. Likewise, a 10-day whole-body exposure to 900 MHz microwave radiation did not cause deficit in the performance of mice in a spatial learning task [12]. A study by Kumin et al. [20] showed that a 5-week exposure to a 900 MHz frequency signal (2 h per day, 5 days a week, SAR 3 W/kg) had no evident effect on the response of young rats in the open field, the plus-maze and the acoustic startle tests. However, in the water-maze test, learning and memory were significantly improved.

Still, there is little data concerning the long-term effects of RF on brain physiology. Epidemiological studies suggested that occupational "low frequency" EMF exposure (such as that associated

Abbreviations: BM, Barnes maze; ELF, extremely low frequency; GSM, global system mobile communication; RF, radiofrequency; SAP, stretched attended postures; SMF, static magnetic field; Tg, unstimulated transgenic mice; TGS, transgenic mice submitted to WIFI stimulation; WT, unstimulated wildtype mice; 3xTg-AD, triple transgenic mouse model of Alzheimer's diseases; WIFI, wireless fidelity; WTS, wildtype mice submitted to WIFI stimulation; EMF, electromagnetic field.

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with power/telephone line maintenance) may increase the risk of Alzheimer's disease (AD) [21]. Other studies investigated acute exposure to "high frequency" EMFs, such as that associated with cell phone usage [22,23]. A number of these studies have, in fact, reported small beneficial effects of acute EMF exposure on attention and/or working memory in normal individuals, although other studies reported no cognitive effects [23].

Antoniazzi and collaborators [24] reported that occupational exposure to RF in women was associated with troubles concerning social relations, anxiety, and depression. In addition, transcranial magnetic stimulation (TMS) is now presented as a potential treatment for depression [8,25] and was demonstrated to enhance coping strategies and to reduce neuroendocrine response in rats subjected to a stressful situation [26].

Our study aimed at investigating the effects of a 4-week exposures to a 2.54 GHz WIFI signal (2 h per day, SAR 1.6 W/kg) on transgenic mice carrying mutations linked with AD (3xTg-AD) in the Flex Field activity system, the Barnes maze and the two-compartment box test.

2. Materials and methods

2.1. Animals

We used triple transgenic mice (3xTg-AD) harboring three mutant human genes associated with AD: Amyloid Beta Precursor protein (APP sw), Presenilin 1 (PS1M146V), and tau P301L. The non transgenic mice (wildtype WT) used here were littermates from the original PS1-knockin mice and were maintained on the same backround as the 3xTg-AD mice (C57BL6/129VJ). The animals were purchased from the Center de recherche du CHUL (CHUQ), Axe neurosciences, Québec, Canada. They were 12 month-old animals (males, a total number of 24). All mice were housed four per cage under standard conditions, maintained on a 12 h dark and 12 h light cycle with ad libitum access to rodent chow and water, randomized and handled under the same conditions by one investigator. All experiments were performed in accordance with the Canadian Council on Animal Care and were approved by the Institutional Committee of the Center hospitalier de l'Université Laval, Canada.

2.2. Experimental exposure to RF signals

Mice were divided into four groups: two groups of transgenic mice, unstimulated and stimulated (TG and TGS), and two groups of wildtype mice, unstimulated and stimulated (WT and WTS) (Fig. 1) ($n = 7$).

WTS and TGS mice exposed to electromagnetic field were housed in cages arranged in a circular pattern in a Faraday cage, with each cage approximately 26 cm from a centrally located EMF-emitting antenna. This antenna was that of an EMF generator (MODEM) tp-link (intensity 2400 MHz and SAR 1.6 W/kg) and provided 2 h periods of EMF per day (at 06:00 a.m.) at 2400 MHz and a whole body SAR of 1.6 W/kg.

Sham-treated animals were located in a completely separate room, with identical room temperature as in the EMF exposure room and with cages arranged in the same circular pattern.

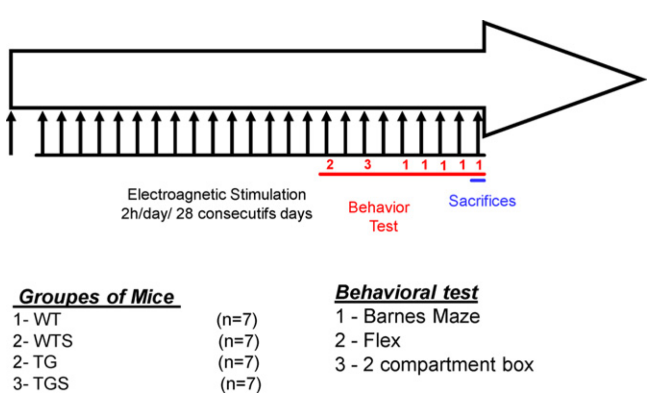

Fig. 1. Electromagnetic stimulation of mouse Alzheimer mouse: experimental design.

2.3. Behavior tests

2.3.1. Barnes maze

Carol Barnes developed a dry-land maze test for spatial learning and memory in 1979 where animals escaped from a brightly lit, exposed circular open platform surface to a small dark recessed chamber located under one of the 18 holes around the perimeter of the platform. Although it was initially invented for rats, the Barnes maze (BM) has become more popular to assess spatial memory in mice, taking advantage of their superior abilities to find and escape through small holes [27,28].

Visual cues are required to optimize cognitive performance in the BM [34]. Kumlin et al. [20], Moser et al. [29] showed better performance in mice tested with intra- and extra-maze cues than mice trained with no spatial cues present. Moreover, rodents with hippocampal damage showed impaired performance in the BM, supporting the spatial nature of the task [30].

The BM presents similarities to the Morris Water Maze and to the radial-arm maze task, but no strong aversive stimuli or deprivation is being used as reinforcement. Instead, weak aversive stimulation may be applied to increase the motivation to escape from the circular platform (e.g., buzzer, light, fan) [21,31]. Strong aversive stimuli (i.e. water or shock) are likely to produce stress in the animal, influencing the performance in the task [32]. Mostly reference memory and working memory have been studied using the BM with different protocols. Here we propose a protocol to study short-term and long-term reference memory in mice.

The animal was first habituated to the Barnes maze by manual guiding into the escape box for about five trial runs. Rodents quickly learn the location of an escape hole using the spatial reference points that are either fixed relative to the maze or are on the maze itself and located relative to the escape hole. After the trial runs, each mouse was permitted to explore the maze freely and its activity monitored while they found the escape hole. Once the rat or mouse entered the escape box, the hole was covered to prevent the animal from re-emerging.

The test was 90 s long and began with the placement of a mouse at the center of the maze, with its head facing an open arm. The time spent and the numbers of entries in the different parts of the maze were recorded, the number of errors prior to locating which one of the 18 arms contained a submerged escape platform was determined for 4 trials per day. The maze was cleaned with a 10% alcohol solution between each animal.

2.3.2. Anxiety tasks: two-compartment box test

Control and SMF-exposed mice were tested in a two-compartment box (Dark and Light box); this test measures the anxiety. Animals were exposed to the apparatus for a single session of 5 min.

At the beginning of the test, the mouse was placed in the dark box. Latency time (time of moving from the dark to the light compartment), number of entries and time spent in the dark box were measured. This test is considered as an approach–avoidance measure and a reliable index of anxiety since it responds to anxiolytic agents and it is sensitive to stress induced anxiety states. In addition, time and locomotion in the two boxes (number of crossings) were measured. The apparatus was also wiped using a 10% alcohol solution before the next animal was introduced, as to preclude.

2.3.3. Flex Field Activity System

The Flex Field behavioral test is the most commonly used method to measure alterations of motor activity after exposure to WIFI signals. It consists of 10 clear walled, plexi-glass, square open arenas with a length of 80 cm and a width of 80 cm. These arenas are attached to an automated photo beam activity system, which tracks movement by recording photo beam breaks (San Diego Instruments, San Diego, CA, USA). This measure directly correlates to the distance traveled, which is a measure of general locomotor activity. Rearing, peripheral and central, ambulatory and fine movements are also recorded with this system. Mice were tested for a one hour period always at the same time of day (2:00 p.m.). The tests were performed in a dark room that was completely isolated from external noises and light during the test period, on day 21 after exposure to EMF.

2.4. Statistical analyses

All results are shown as means ± standard errors of the mean (S.E.M). Unpaired ANOVA with repeated measures were conducted using Graph Pad Prism (version 5.0). Differences were considered as significant for p values below 0.05.

3. Results

3.1. Effects of WIFI signals on body weight

Body weight was monitored during the 28 days of exposure to WIFI signals (starting at 12 months of age). As shown in Fig. 2, no significant difference in body weight was observed during the entire exposure period between: WT/WTS, WT/TG, WT/TGS and TG/TGS.

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