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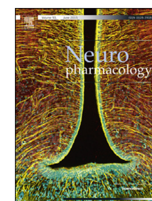

Improvement of spatial learning by facilitating large-conductance calcium-activated potassium channel with transcranial magnetic stimulation in Alzheimer's disease model mice

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A B S T R A C T

Transcranial magnetic stimulation (TMS) is fragmentarily reported to be beneficial to Alzheimer's patients. Its underlying mechanism was investigated. TMS was applied at 1, 10 or 15 Hz daily for 4 weeks to young Alzheimer's disease model mice (3xTg), in which intracellular soluble amyloid-β is notably accumulated. Hippocampal long-term potentiation (LTP) was tested after behavior. TMS ameliorated spatial learning deficits and enhanced LTP in the same frequency-dependent manner. Activity of the large conductance calcium-activated potassium (Big-K; BK) channels was suppressed in 3xTg mice and recovered by TMS frequency-dependently. These suppression and recovery were accompanied by increase and decrease in cortical excitability, respectively. TMS frequency-dependently enhanced the expression of the activity-dependently expressed scaffold protein Homer1a, which turned out to enhance BK channel activity. Isopimaric acid, an activator of the BK channel, magnified LTP. Amyloid-β lowering was detected after TMS in 3xTg mice. In 3xTg mice with Homer1a knocked out, amyloid-β lowering was not detected, though the TMS effects on BK channel and LTP remained. We concluded that TMS facilitates BK channels both Homer1a-dependently and -independently, thereby enhancing hippocampal LTP and decreasing cortical excitability. Reduced excitability contributed to amyloid-β lowering. A cascade of these correlated processes, triggered by TMS, was likely to improve learning in 3xTg mice.

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1. Introduction

Beneficial effects of transcranial magnetic stimulation (TMS) on cognitive functions have been demonstrated in normal human subjects (Cappa et al., 2002), elderly people with memory dysfunction (Rossi et al., 2004; Solé-Padullés et al., 2006), and Alzheimer's disease (AD) patients (Cotelli et al., 2006; Ahmed et al., 2012). However, neurobiological grounds of TMS effects have been studied largely in the context of antidepressant treatment by using animal models (Fleischmann et al., 1995; Zyss et al., 1997; Müller et al., 2000; Keck et al., 2001; Ikeda et al., 2005; Kim et al., 2006; Sun et al., 2011). By contrast, neurobiological evidence that might support a therapeutic application of TMS to AD is lacking. It is reported that exposure to very weak high-frequency electromagnetic field (918 MHz), such as the one emitted from a cellular phone to the phone caller, improves cognitive deficits and reduced Aβ burden in AD model mice (Arendash et al., 2012), though this procedure and TMS are different. TMS is shown to induce or modulate synaptic plasticity in normal rodents or rabbits (Wang et al., 1996; Levkovitz et al., 1999; Ogiue-Ikeda et al., 2003) and in aging rats as well (Levkovitz and Segal, 2001), but not yet in AD model animals. Above all, it has not been behaviorally tested whether TMS ameliorates learning in AD model mice. This was therefore examined in the present study.

Insoluble deposits of amyloid plaques and neurofibrillary tangles in brain tissue have been considered most causative of

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Alzheimer's disease (AD) since Alzheimer's original description (Goedert and Spillantini, 2006; Hardy, 2006; both for review). However, recipients of anti-amyloid vaccination appear to have failed to exhibit correlation of cognitive amelioration and plaque clearance (Schenk et al., 1999; Holmes et al., 2008). In model mice, cognitive impairment is often manifested before age-dependent appearance of amyloid deposits (Oddo et al., 2003). Although the correlation between clearance of Aβ plaques and cognitive recovery is demonstrated in model mice (Cramer et al., 2012), soluble Aβ has also been a focus of attention as a key to link cognitive dysfunction and underlying molecular events in AD pathogenesis (Hardy and Selkoe, 2002; Kamenetz et al., 2003; Haass and Selkoe, 2007; Brody and Holtzman, 2008), especially at its early phase. Intracellular soluble Aβ is regarded as one of the early pathological events in AD (Oddo et al., 2003; Gouras et al., 2000). Recently we have found that intracellular Aβ suppressed a class of potassium channel, the large conductance calcium-activated potassium (Big-K; BK) channel (Yamamoto et al., 2011). This channel was shown to be facilitated by TMS in depression model mice (Sun et al., 2011). In the present study, it is therefore of our particular interest to investigate whether TMS effects on AD model mice that we hypothesize might be achieved through a functional reversal of Aβ-induced suppression of BK channels. For this purpose, we used 4-to-5-month-old 3xTg model mice (Oddo et al., 2003), in which intracellular soluble Aβ is notably accumulated prior to the extracellular deposit of amyloid plaques (LaFerla et al., 2007).

2. Materials and methods

2.1. Animals

All the experiments were performed in accordance with the guiding principle of the Physiological Society of Japan and with the approval of the Animal Care Committee of Kanazawa Medical University. Triple transgenic AD model mice (3xTg) with 129/C57BL6 hybrid background (Oddo et al., 2003), provided from Dr LaFerla (University of California, Irvine), were kept in group cages in our in-house colony under an automatic day–night control (12:12 h), and allowed free access to food and water. Male 3xTg mice of 4–5 months of age at the beginning of the experiment were used. Mouse ages at the time of different experiments are illustrated in Fig. 1. As the age-matched control, non-transgenic mice from the same hybrid background were used (wild-type). To introduce homozygous Homer1a knockout into 3xTg mice, transgenic mice that lack the Homer 1a isoform specifically but not the Homer 1b/c isoforms (Inoue et al., 2009), provided from Dr Inokuchi (Toyama University, Toyama), were crossed with 3xTg mice and backcrossed more than 5 generations.

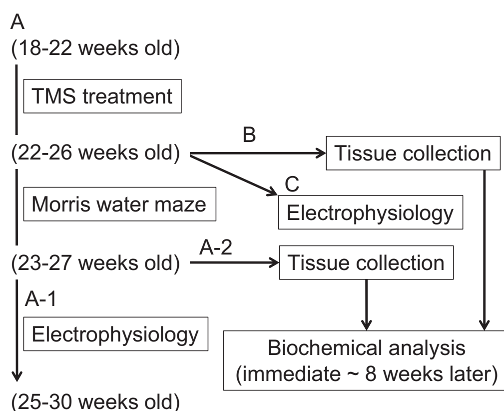

Fig. 1. Diagram showing the time course of experiments. The majority of mice, following the time schedule indicated on the left-most (A), were first treated with TMS or sham procedure, second subjected to the Morris water maze test (MWM), and finally used to collect hippocampi and cerebral cortices for immediate electrophysiological experiments (A-1) or later biochemical analyses (A-2). Tissue for biochemistry was immediately frozen with liquid nitrogen and stored at −80 °C (A-2). We sometimes used one hemisphere for slice experiments and the other for later biochemical experiments. The other mice were used for electrophysiological or biochemical analyses immediately after TMS treatment without MWM (B, C). We noticed no systematic influences attributable to performing the behavioral test. In addition, LTP experiments with Iso application were done in slices prepared from naïve 3xTg mice of 20–22 weeks old.

2.2. Behavioral studies

The Morris water maze test was performed by using plastic cylindrical tank (120 cmφ) that is surrounded by a wall of 45 cm high and filled with opaque water (25 °C). A transparent plastic platform (10 cmφ) was hidden below the water surface with its base fixated to the floor of the tank. Four large, differently-colored objects were placed above the edge of the tank as geographical external cues. On each of 5 consecutive days, mice were given 4 sessions of swim. For each session, the mice were released from a starting point pseudo-randomly chosen from the 4 prefixed positions, and the time spent to reach the platform (escape latency) was measured. If mice were not able to reach the platform within 60 s, they were placed on the platform by the experimenter and allowed to stay there for 60 s. The average of the time spent over the 4 sessions yielded the latency score for a particular day for an individual mouse. The day-by-day averages were then calculated for each group. Swimming trajectory was video-taped and analyzed off-line (SMART, Panlab s.l.u., Cornella, Spain). After the last goal-seeking session on the last test day, the platform was removed to perform the probe test. The animals were placed into the water from the edge of the pool located opposite to the former platform position, and allowed to swim for 1 min. The swimming trajectory was video-taped and analyzed off-line by SMART software. The time spent in the target quadrant was calculated and expressed as percentage over the total time of 1 min.

2.3. Transcranial magnetic stimulation (TMS)

TMS was done as described (Sun et al., 2011). With a magnetic stimulator (Magstim Rapid, MRS1000/50, Magstim Company Ltd, Whitland, UK), biphasic magnetic pulses were delivered: the pulse uprise time, 60 μs; duration, 250 μs. The strength of the pulse was 80% of the maximum output of the machine. Animals were gently held by hand with the aid of a plastic cylinder, and then a small figure-8-shaped coil for rodents (5 cmφ) was placed over the skull with a direct contact to the head skin. Stimulation intensity was as large as to cause muscle twitch in the lower extremities, which was detected manually by the experimenter. Chronic TMS was applied daily at 1, 10 or 15 Hz for 5 s once a day for 4 weeks. Sham-treated mice were handled similarly to those treated with TMS and heard the click sound at 15 Hz, but did not receive stimulation. These sham-treated 3xTg and wild-type mice were used as the control, not just for the 15-Hz-TMS groups but also for the 10- and 1-Hz-TMS groups. The experiments were performed in a blind manner with regard to the genotype and treatment.

2.4. Slice experiments

Mice used for behavioral studies were sacrificed by decapitation under ether anesthesia. In addition, some mice were used solely for behavior or for electrophysiological experiments. The brain was dissected out and soaked into medium (pH 7.4; 2–5 °C) containing (in mM): NaCl 124, KCl 3.3, KH_2PO_4 1.3, $NaHCO_3$ 26, $CaCl_2$ 2.5, $MgSO_4$ 2.0, and glucose 10. Slices of the bilateral hippocampi (400 μm thick) and cingulate cortex (200 μm thick) were cut with a slicer (Zero-1, Dosaka, Kyoto, Japan). Hippocampal slices were used for experiments on long-term potentiation, paired-pulse facilitation and normal synaptic transmission, whereas assessment of excitability and BK channel activity was done in cingulate cortex slices. Cingulate cortex slices were placed in a recording chamber on the stage of an upright microscope (Eclipse E600FN, Nikon, Tokyo, Japan) with a 40× water immersion objective (Fluor 40× 0.80 W, Nikon). The chamber was continuously perfused with medium (25°C) bubbled with a mixture of 95% O_2 and 5% CO_2. Patch recording was done as described (Yamamoto et al., 2011; Sun et al., 2011). Whole-cell recordings were made from cingulate cortex layer II/III pyramidal cells that had sufficiently negative resting membrane potentials (<−55 mV) without spontaneous action potentials. Membrane potentials were recorded in the current-clamp mode (Axoclamp 200A and B, Molecular Devices, California, USA), digitized at 10 kHz (Digidata 1322, Digidata 1440, and pCLAMP10, Molecular Devices), and analyzed off-line with Windows-based PCs.

To evaluate membrane excitability, depolarizing currents (0.05–0.5 nA for 500 ms) were injected into recorded neurons. Currents were injected every 1 min to evoke spikes. The firing pattern was typical to regular-spiking neurons. For spike width measurement, a train of five pulses of depolarizing currents were injected at 100 Hz. The duration (4–5 ms) and intensity of injected current were adjusted so that each pulse evoked a single spike. The time point of spike initiation was easily determined because of a clear deflection of the membrane potential at the transition from the passive to active phase of voltage rising. Based on the voltage at this spike initiation and that at the peak, the spike half height was calculated. On the depolarizing and repolarizing phases of the spike, the two time points corresponding to this spike half height were determined. The spike half width was defined as the time length between these two time points.

For field potential recordings at Schaffer collateral-CA1 synapses, recording electrodes (2–5 MΩ) filled with 2.5 M NaCl were placed in the stratum radiatum and a set of bipolar tungsten electrodes was inserted nearby in hippocampal slices. To

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