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Aging affects transcranial magnetic modulation of hippocampal evoked potentials

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Abstract

Transcranial magnetic stimulation (TMS) is being proposed as a method of choice for the treatment of clinical depression, yet its action in the brain is still not well understood. In previous studies we found that TMS has a long-term effect on reactivity of the hippocampus to perforant path stimulation. Since the efficacy of antidepressants is highly age-dependent, we studied possible age-related effects of TMS on hippocampal evoked responses. Young adult (3 months), aging (10 months) and aged (24–26 months) awake rats were subjected to daily TMS for one week, followed by measurements of several parameters of reactivity to perforant path stimulation in the anesthetized rat. TMS did not affect responses of the hippocampus to single perforant path stimulation, but reduced drastically paired-pulse and frequency dependent depression in the young and aging but not the old rats. Likewise, TMS increased LTP expression in the young but not the old rats, and reduced the efficacy of serotonin modulation of reactivity of the hippocampus, in the young but not the old rats. Thus, long term effects of chronic TMS on local GABAergic inhibition are highly age dependent. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Transcranial magnetic stimulation; aging rats; dentate gyrus; serotonin; LTP; GABAergic inhibition

1. Introduction

Depression is a prominent psychiatric disorder in the elderly [7,13,21,23,38]. Serotonin-specific reuptake inhibitors (SSRI) and tricyclic antidepressant (TCA) are in general less effective in treating depression in aged patients than in their younger counterparts [31]. In the elderly patient, the time required for the improvement of depressive symptoms with antidepressant therapy has been reported to be as long as 6–12 weeks [3,10]. This pattern of reduced therapeutic efficacy is characteristic of SSRI and TCA and involves an age-related decline in the serotonergic neuronal system [8,38]. Age-related alterations in the synthesis, release, and turnover of serotonin [16,39,40] 5-HT receptor density [2,11,30], density of the 5-HT transporter [1,42] as well as physiological sensitivity to serotonergic agonists [6,26–27] have also been described.

While several brain regions have been associated with emotional symptoms of depression, one of the most frequent symptoms, cognitive dysfunction, was repeatedly associated with hippocampal atrophy [24,35–37]. The volume loss in the hippocampus is related to memory function and significantly correlated with total lifetime duration of depression (34–37). The cognitive deficits are features commonly associated with aging. Thus, the hippocampus, heavily innervated by serotonergic fibers arising from the raphe nuclei, is an attractive target for the analysis of the effects of antidepressive treatments on elderly brain physiology.

Transcranial magnetic stimulation (TMS) is a new non-invasive, fairly safe method for stimulation of the brain [4,5]. Magnetic stimulation of the human brain is increasingly used for functional cortical mapping of primary motor areas and for the investigation of cortical function related to cognition in both health and disease states [5,14,19]. TMS has been suggested recently for the treatment of psychiatric disorders of mood and emotional dysfunction. Clinical studies [15,17,20,22] suggest an antidepressant efficacy for TMS in depressed human patients.

In earlier studies we found long-lasting effects of TMS on reactivity of the hippocampus to stimulation of its main excitatory afferent pathway arising from the entorhinal cortex, the perforant path [29]. Chronic TMS, similar to two

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other antidepressive drugs, desipramine and mianserine, did not affect single population spikes but caused an increase in paired -pulse potentiation, which was still evident 3 weeks after the last of a series of daily TMS treatments. Serotonergic and noradrenergic modulation of evoked synaptic activity may be related to these long-term TMS effects on synaptic transmission in the hippocampus.

The objectives of the present study are to test the hypothesis that aging retards the efficacy of TMS in modulating inhibitory circuits of the hippocampus, and their regulation by monoamines.

2. Materials and methods

2.1. Animals. Experiments were conducted with young (3 months old), aging (10 month) and old (24–26 months) Long-Evans rats of a local breeding colony. Each age group was divided randomly to control and chronic TMS-treated rats. The rats were housed in a temperature-controlled room, three-four rats to a cage, with 12 h light/dark cycle and free access to food and water.

2.2. TMS. One millisecond pulses were applied with a Cadwell (Kennewick, WA). Rapid Stimulator at a frequency of 25Hz for 2 s with a field intensity of 2.2 tesla (at 100% current intensity; flowing clockwise; calculated between 1–1.5 cm from the center coil [19]; estimated peak electric field strength of 660 V/m) through a 5 cm coil with a teardrop shape. Using these stimulation parameters, the hippocampus and posterior cortex are likely to be stimulated irrespective of the thickness of the skull [19]. The awake rat was held gently by hand while the coil was placed above the head, aligned with its center on the midline, equidistant between the bregma and lambda sutures along the longitudinal body axis. Rats were stimulated once daily for 7 days. Control rats were handled the same way as the treated ones and were exposed to the same noise produced by the stimulator.

Two days after the last day of TMS stimulation rats were anesthetized with urethane (21% solution, 1.2 gm/kg, i.p.) and placed in a stereotaxic apparatus. A bipolar, 125 μm concentric stimulating electrode was placed in the perforant path (PP) (coordinates: 7.5 mm posterior to bregma, 3.0 mm lateral to the midline, depth of 3.5 mm), and a single glass pipette (diameter of 2–3 mm) containing 2M NaCl was advanced into the dentate gyrus of the dorsal hippocampus using an hydraulic microdrive. Electrode positions were optimized to record maximal population spike (PS) in response to 100 μsec pulse stimulation of the medial PP. Evoked responses were amplified and filtered at 1 Hz- 1 kHz and stored for later analysis.

2.3. Paired-pulse inhibition. A twin pulse PP stimulus was delivered at three interpulse intervals (15, 30 and 60 msec), and averages of 5 successive response to a given intensity applied at a rate of 0.5 Hz were constructed. Paired-pulse response was quantified as the magnitude of the second over the first PS or the slope of the second EPSP over the first one.

2.4. Frequency dependent inhibition. Two series of stimuli were delivered, each series includes twenty stimuli at 1 Hz and twenty stimuli at 0.1 Hz, with baseline recorded again between the two series. PS and EPSP were measured as the average of forty stimuli at the same frequency relative to prior baseline condition. Differences in PS and EPSP between the two frequencies were quantified as the second minus the first PS (PS 0.1 Hz-PS 1 Hz) or the slope of the second minus the first slope (EPSP 0.1 Hz - EPSP 1 Hz).

2.5. LTP Induction. After electrode insertion, input-output relations, paired-pulse stimulation and frequency dependent inhibition were obtained, recording was made for 15 min followed by 10 min of baseline recording, before tetanic stimulation was applied. The LTP-inducing stimulation intensity was at 50% of the level that could evoke the maximum asymptotic spike amplitude. The parameters for the stimulation to induce LTP were 10 trains with an inter-train interval of 1 s and each train consisting of eight 0.4 ms 400 Hz pulses. LTP in each experiment was assessed as the change in response measured 35–40 min after tetanus and expressed as a percentage of the mean of the 20 responses obtained during the 10 min preceding the tetanus.

2.6. Serotonergic modulation. Seventy minutes after the tetanic stimulation, serotonergic modulation of PS was measured using the serotonin releaser, fenfluramine (FFA, 7.5 mg/kg, i.p, see 34 for details) PS and EPSP were measured 15 and 25 min after FFA injection.

2.7. Analysis. Off-line measurements of the slopes of the EPSPs (in volts per second) and magnitudes of the maximal population spike (in millivolts) were made from averages of 5 successive responses to a given stimulation intensity applied at a rate of 0.1 Hz. PS size and EPSP slope were measured as describe previously [28]. To standardize the calculations and minimize cross-animal variability, the magnitudes or slopes of all responses were expressed as percentage of the asymptotic response obtained at control conditions with maximal stimulation (100%). The normalized data were analyzed statistically with SPSS 8.0 statistical package using three-way analysis of variance (ANOVA), with repeated measures, i.e. stimulus intensity or interpulse interval (IPI), on one of the variables (age and treatment), followed by Schaffer post-hoc multiple comparisons. Significance level was set at 5%. In some cases, *t* tests were used for the comparisons between specific groups.

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