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Repetitive Transcranial Magnetic Stimulation (rTMS) increases Plasma Calcium both *in vivo* and *in vitro*

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Abstract

Background: We have previously demonstrated that brain levels of gamma-aminobutyric acid (GABA) were diminished in patients with various types of dysgeusia and dysosmia by use of magnetic resonance spectroscopy (MRS). We also demonstrated by use of functional magnetic resonance imaging (fMRI) of brain that when these patients were requested to think of their dysgeusia or dysosmia they exhibited significant brain activation in specific brain regions. Treatment with repetitive transcranial magnetic stimulation (rTMS) increased brain levels of GABA as measured by MRS and decreased brain activation as measured by fMRI. These changes were accompanied by increased levels of plasma, erythrocyte and saliva zinc and copper after rTMS.

Purpose: To evaluate if changes in plasma calcium, either *in vivo* or *in vitro*, also occurred in these patients after rTMS.

Methods: Measurements of plasma calcium, *in vivo* and *in vitro*, were measured in 129 patients with dysgeusia and dysosmia before and after rTMS.

Results: Both *in vivo* and *in vitro* levels of plasma calcium increased significantly after rTMS although levels *in vivo* were higher than *in vitro*. These changes occurred in both men and women.

Conclusions: These results, as in previous studies with zinc and copper, indicate that electromagnetic fields increase calcium levels. These studies are the first which describe increased levels of plasma calcium both *in vivo* and *in vitro* in humans treated with rTMS. These changes are consistent with changes in neuroplasticity that relate to the role that rTMS plays in calcium metabolism related to changes in GABA and other neurotransmitters.

Keywords: Transcranial magnetic stimulation; Calcium; Dysgeusia; Dysosmia; Neuroplasticity

Introduction

Patients with dysgeusia and dysosmia (distortions of taste and smell, respectively) of several types exhibit significant activation in specific brain regions when measured by functional magnetic resonance imaging (fMRI) of brain [1]. Evaluation of this activation by use of magnetic resonance spectroscopy (MRS) revealed that while this brain activation was extremely robust and widespread [1] levels of the inhibitory transmitter gamma-aminobutyric acid (GABA) were significantly diminished [2]. Treatment which increased these low levels of brain GABA with either GABAergic drugs [2] or repetitive transcranial magnetic stimulation (rTMS) of brain [3] inhibited these sensory distortions [2,3], inhibited the robust activation previously measured in the untreated state using fMRI [1] and inhibited the dysgeusia and dysosmia [4]. These events were related to effects of rTMS on neuroplasticity [5].

Transcranial magnetic stimulation (TMS) has been reported to influence several neurotransmitters and neuroactive substances including dopamine [6-11], biogenic amines [12-14], serotonin [15-17], GABA [18-20], 5-HIAA [21] and interactions among these moieties [7,14]. rTMS has been reported to modify central nervous system excitability [11,22-26], to enhance sensory function [27], to alter cognition [28-32] and to alter concentrations of several neurotransmitters, as noted above. TMS has also been reported to be useful in several neurological conditions including rehabilitation after ischemic stroke [33,34], decreasing some symptoms of Parkinson's disease [35,36], improving auditory hallucinations in patients with schizophrenia in some [37,38] but not in other studies [39] and inhibiting tinnitus [19,40]. In a prior study we demonstrated that rTMS improved taste and smell dysfunction through a putative role in modulating central nervous system plasticity [3-5,41].

In an effort to understand more about the biochemical changes which might relate to these dramatic neurological changes we evaluated changes in plasma, erythrocyte and saliva zinc and copper, in erythrocyte carbonic anhydrase I, II and in the neurotransmitter carbonic anhydrase VI in saliva after rTMS [42]. Results of these studies demonstrated that after rTMS was used in patients with dysgeusia and dysosmia levels of their plasma, erythrocyte and saliva zinc and copper, erythrocyte carbonic anhydrase (CA) I, II and saliva CA VI increased [42].

Further analysis of these and similar studies revealed that changes in plasma calcium accompanied these changes in zinc, copper and CA. While we had no prior indication that changes in plasma calcium might be related to treatment with rTMS we now present studies in which rTMS increased plasma calcium levels both *in vivo* and *in vitro* in patients with various types of dysgeusia and dysosmia.

Methods

Study design

This was a prospective sham controlled, fixed sequence, open clinical trial conducted between June, 1999 and January, 2014. Changes in sensory acuity, distortions, and plasma calcium before and after rTMS were measured. This study was approved by the IRB of the George Washington University Medical Center.

Patients

One hundred and twenty-nine patients, 55 men, aged 40-74y (58 ± 7 y, Mean ± SEM), 74 women, aged 30-76 y (51 ± 5 y) were studied at The Taste and Smell Clinic (The Clinic) and at the Department of Neurology at the George Washington University Medical Center, both in Washington, DC. Each patient had mild to severe dysgeusia and dysosmia which was characterized by persistent birhinal phantosmia (a distorted odor in the nose in the absence of any external odor [1,3,43]) and/or global oral phantageusia (a distorted taste in the mouth in the absence of any oral stimulus [43,44]), aliageusia (a distorted taste associated with intake of any food or drink [43,44]) and/or aliosmia (a distorted smell associated with the presence of any external odor [43]) which were profound and interfered with normal life pursuits. Each patient also had mild to severe persistent hyposmia (smell loss as measured by olfactometry [43]) and hypogeusia (taste loss as measured by gustometry [43]). Prior to this study sensory distortions persisted for 3 mo to 30 y (3.7±2 y); taste and/or smell loss persisted for 6 mo to 30 y (4.1±2y). Etiologies which initiated these symptoms were head injury [45] (30 patients), post influenza-like infection (PIHH [46]) (54 patients), idiopathic causes [47] (30 patients) and drug reactions [48] (15 patients). Each patient who presented to The Clinic with these symptoms was treated with rTMS. All studies were consistent with the protocol approved by the IRB of the George Washington University Medical Center to which all patients agreed.

None had either clinical otolaryngological or neurological symptoms other than loss of sensory acuity and presence of sensory distortions. None had any psychiatric symptom other than some depression associated with persistence of these sensory impairments. Physical examination of each patient including examination of the head and neck and general neurological examination was within normal limits. Both anatomical brain MRI and electroencephalograms were within normal limits.

An entire battery of sensory measurements (olfactometry and gustometry as identified above [43]) was obtained at the initial patient visit to The Clinic and repeated immediately prior to and after rTMS. Each test battery and rTMS trial [4] was performed independent of knowledge of any prior result.

Treatment protocol

rTMS was performed with a Cadwell (Kennewick, WA) magneto-electric stimulator MES-10 monitored by a TECA TD20 (Pleasantville, NY) wave form generator. Stimulation was applied by use of a single circular 5 cm (internal diameter) coil [4].

Three consecutive stimulation procedures were used at each rTMS trial [4]. The first two were sham procedures, the third was the real trial. Each procedure consisted of the patient viewing the stimulating instrument and, with each activation and disappearance of the signal, visualizing the on and off appearance of a green light and hearing on and off sound of the activity stimulus click.

Prior to this procedure blood was obtained by venipuncture and placed into each of two acid washed glass tubes containing 100 µl heparin. One tube was centrifuged at 3000xg for 10-15 min. The plasma contents of this tube were aspirated and saved at 4°C for measurements of plasma calcium. The contents of the second tube were placed in ice and treated with rTMS *in vitro* as noted below.

The first rTMS procedure was a sham procedure consisting of applying 20 stimuli at intervals of 1-5 sec at 25-35% maximal output [25-35% of 1.5T or ~0.3-0.5T (since stimulus delivery was non-linear)] sequentially (a) to the anterior right shoulder, [at the lateral acromial process of the clavicle (near Erb's point)] then (b) anterior left shoulder (near Erb's point) and then (c) to the back of the mid neck region (at the level of C5-8 at 30-40% maximal output or ~0.4-0.8T); mild to moderate muscle group flexion of arm and hand muscles (shoulder stimulation) and neck, strap and facial muscles (neck stimulation), respectively, followed stimulation at each respective site and was visually monitored [4].

The second rTMS procedure was another sham procedure consisting of applying 20 stimuli at intervals of 1-5 sec at 10-15% maximal output (10-15% of 1.5T or ~0.08-0.15T, a subthreshold stimulus) sequentially to four skull regions in a fixed sequence (left temporoparietal, occipital, right frontoparietal, frontal). No subjective or peripheral muscle response occurred in response to this stimulation [4].

The third rTMS procedure was the real trial consisting of applying 20 stimuli at intervals of 1-5 sec at 40-55% maximal output (~0.8-1.1T) sequentially to each skull location as in the second sham procedure noted above. Right/left thenar and/or phalangeal flexion after left/right temporoparietal stimulation, respectively, occurred and was monitored by visual observation. Mild facial muscle flexion usually occurred after occipital stimulation and bilateral eye blinking usually occurred after frontal stimulation [4].

After this third procedure venipuncture was again performed, the blood transferred to another acid washed glass tube containing 100 µl heparin, centrifuged at 3000xg in a refrigerated centrifuge for 10-15 min, the plasma removed and stored at 4°C until assayed. This sample was labeled the *in vivo* plasma sample. At this time, the second tube previously obtained was treated with direct application of the same rTMS procedure applied to one of the skull regions noted above in the third rTMS procedure. This consisted of applying 20 stimuli at intervals of 1-5 sec at 40-55% of maximal output directly to the top of the tube as it was placed in an ice bath. After this stimulation this tube was centrifuged at 3000xg in a refrigerated centrifuge for 10-15 min, the plasma aspirated and stored at 4°C to be assayed. This sample was labeled *in vitro* sample and all *in vitro* results relate to measurements obtained using this plasma sample.

Measurement procedures

Plasma from each of the three tubes was analyzed by flame aspiration atomic absorption spectrophotometry (AAS) on a Thermo Jarrell Ash AAS modified by the Maxwell Instrumentation Company (Salisbury, NC) by a variation of the method previously developed for measurement of zinc and copper [49] and approved and monitored by the Clinical Laboratory Improvement Amendments (CLIA) of the U.S. government.

Statistical analysis

All studies were performed independent of any knowledge of the treatment condition of any patient. Since each patient had collection of plasma performed before rTMS and after both *in vitro* and *in vivo* rTMS treatment paired comparisons of analysis were performed for each patient group with results considered significant using Student's t-test with $p<0.05$.

Results

Significant increases in plasma calcium occurred after rTMS both *in vivo* and *in vitro* (Table 1). *In vivo* levels were about 10% higher than *in vitro* levels.

Condition	Plasma calcium (mg/dl)
Pre rTMS	9.29 ± 0.04*
rTMS Irradiation (*in vitro*)	9.35 ± 0.04a
Post rTMS (*in vivo*)	9.39 ± 0.04b
With respect to Pre rTMS (by paired comparison): a p<0.01; b p<0.05 * Mean±SEM	

Table 1: *In vivo* and *in vitro* changes in plasma calcium before and after rTMS in 129 patients with dysgeusia and dysosmia.

Condition	Plasma calcium (mg/dl)
Pre rTMS (*in vivo*)	
Men	9.31 ± 0.05*
Women	9.28 ± 0.05
rTMS Irradiation (*in vitro*)	
Men	9.35 ± 0.06
Women	9.36 ± 0.06
Post rTMS (*in vivo*)	
Men	9.43 ± 0.06b
Women	9.35 ± 0.06
With respect to Pre rTMS (by paired comparison): b p<0.05 * Mean±SEM	

Table 2: *In vivo* and *in vitro* changes in plasma calcium before and after rTMS in 55 men and 74 women with dysgeusia and dysosmia.

When analyzed by gender, increases in plasma calcium occurred after rTMS in both *in vivo* and *in vitro* studies although increases were significant only for men after *in vivo* rTMS (Table 2). There were no significant differences under any condition in plasma calcium between men and women.

When analyzed by age, increases in plasma calcium occurred after rTMS in both *in vivo* and *in vitro* studies although levels were generally not significantly increased except for comparisons of *in vivo* studies pre and post rTMS in the 31-50 y age group (Table 3).

Condition	Plasma calcium (mg/dl)
Pre rTMS [*in vivo*]	
10-30 years (4)	9.50 ± 0.13*
31-50 years (18)	9.31±0.09
51-70 years (75)	9.30±0.05
71-90 years (32)	9.26 ± 0.09
rTMS Irradiation [*in vitro*]	
10-30 years (4)	9.78 ± 0.09
31-50 years (18)	9.39 ± 0.09
51-70 years (75)	9.33 ± 0.05
71-90 years (32)	9.34 ± 0.10
Post rTMS [*in vivo*]	
10-30 years (4)	9.73 ± 0.11
31-50 years (18)	9.31 ± 0.09
51-70 years (75)	9.30 ± 0.05
71-90 years (32)	9.33 ± 0.09
With respect to Pre rTMS (by paired comparison): b p<0.05 * Mean±SEM; ( ) Number of patients	

Table 3: *In vivo* and *in vitro* changes in plasma calcium before and after rTMS in patients with dysgeusia and dysosmia characterized by age.

Discussion

It is of interest that increased plasma calcium occurred after both *in vivo* and *in vitro* studies with use of rTMS. The mechanism(s) by which these changes occurred are complex. *In vitro* studies involved rTMS treatment of whole blood by which cellular calcium was evidently released into the plasma. Previous studies have demonstrated that pulsed magnetic field effected calcium dependent function in several tissues [50] with several studies demonstrating that low energy electromagnetic fields (EMF) elicit changes in calcium levels [51-55]. EMF increases net calcium flux in rat lymphocytes [53,54] with increased free calcium derived from human T-cells [54]. Magnetic fields have been shown to influence molecular events in signal transduction in T cells in which intracellular calcium is involved [54].

On the other hand, *in vivo* studies involved increased plasma calcium as a result of rTMS stimulation to patients at specific brain regions. These results are consistent with the changes elicited by

application of EMF to human astrocytoma cells [51], increasing net calcium flux and cytosolic calcium concentrations in osteoplast-like cells [52], in human hepatoma cells [53] and in magnetic field effects on calcium fluxes which inhibited apoptosis in human glioblastoma cells [56]. Although all studies did not demonstrate these effects [57,58] the present studies and many others indicate that calcium is involved in mediation of field effects which can also involve the immune system [59].

The neurological effects we have demonstrated after brain application of rTMS in these *in vivo* studies have been associated with significant increases in brain GABA [2,3] which enhanced neuroplasticity. Magnetic fields have also been shown to enhance neuronal calcium dynamics which has been considered to play an important role in induction and maintenance of neuroplasticity [60]. Even minor changes in calcium regulation can alter nervous system activity [61]. These changes have also been associated with effects of calcium on the signal transduction cascade [62] not only on brain GABA but also cAMP [63], calmodulin [64] and c-MYC mRNA induction [65].

We have previously demonstrated that application of rTMS to the brain inhibits dysgeusia and dysosmia [4] consistent with its effect on neuroplasticity [5,66] as previously shown in several studies involving these patients [2,3,5]. The concentration of calcium is a major regulator of glutamic acid decarboxylase (GAD) activity [67] and GABA receptors show a close homology to the calcium sensory receptor which responds to changes in extracellular calcium [68]. Calcium channels serve as part of the GABA release system from striatal brain slices [69]. Thus, the increases we have observed in plasma calcium after rTMS may be a manifestation of a complex system in which calcium not only plays a significant metabolic role but also a role in neuroplasticity such as we have observed with the inhibition of dysgeusia and dysosmia.

Conclusion

rTMS inhibits dysosmia and dysgeusia in patients with these symptoms and increases their plasma calcium both *in vivo* and *in vitro*. These changes may relate to changes in calcium metabolism and levels of GABA and other neurotransmitters that are affected by rTMS and influence neuroplasticity.

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