

Cortical excitability in patients with resistance to thyroid hormone compared to patients with hypothyroidism and euthyroid controls: a transcranial magnetic stimulation study

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ABSTRACT

Resistance to thyroid hormone (RTH) describes a rare syndrome in which serum levels of thyroid hormones are elevated but serum levels of thyroid stimulating hormone (TSH) are unsuppressed. The importance of thyroid hormones for the normal function of the adult brain is corroborated by the frequent association of thyroid dysfunctions with neurological and psychiatric symptoms. In this study we investigated whether adult thyroid hormone resistance affects cortical excitability and modulates inhibitory and excitatory intracortical circuitries by using transcranial magnetic stimulation. Cortical excitability was probed with transcranial magnetic stimulation in 4 patients with thyroid hormone resistance, 10 patients affected by overt hypothyroidism (OH) and 10 age-matched healthy controls. We tested motor thresholds, motor evoked potential recruitment curve, cortical silent period (CSP), short interval intracortical inhibition (SICI) and intracortical facilitation. In both OH and RTH patients, the inhibitory cortical circuits were affected compared with euthyroid controls, but in opposite ways. In OH patients, CSP was prolonged and SICI was decreased. On the contrary, in RTH patients CSP was shortened and SICI was increased. Thyroid hormones may influence cortical excitability and cortical inhibitory circuits.

Key words

Resistance to thyroid hormone • Hypothyroidism • Cortical excitability • Transcranial magnetic stimulation

Introduction

Resistance to thyroid hormone (RTH) is a rare autosomal dominant inherited syndrome of reduced end-organ responsiveness to thyroid hormone. Patients with RTH have elevated serum thyroid hormone concentrations (both FT4 and FT3) and a

inappropriately normal or slightly elevated serum TSH (Olateju and Vanderpump, 2006; Refetoff and Dumitrescu, 2007; Ferrara et al., 2012; Dumitrescu and Refetoff, 2013b). RTH is mainly caused by germline mutations of the β isoform of the thyroid hormone receptor (TR β). However, depending of the TR isoform (β or α) mutated or the absence of

mutation in either isoform, RTH is now classified into three types, RTH β , RTH α , and nonTR-RTH (Dumitrescu and Refetoff, 2013b; Weiss et al., 1996). The mutations, which usually confer a decreased binding affinity for the ligand T3, interfere with the capacity of the corresponding wild-type TR to respond normally to T3 (Dumitrescu and Refetoff, 2013a-b). Despite a variable clinical presentation, the common clinical features of the RTH syndrome are the presence of goiter but the absence of the usual symptoms and metabolic consequences of thyroid hormone excess, except tachycardia. One half of patients with RTH shows some degree of learning disability with or without attention deficit hyperactivity disorder (ADHD) (Dumitrescu and Refetoff, 2013b; Hauser et al., 1993). One-quarter have intellectual quotients less than 85% even if frank mental retardation has been found only in few cases. Impaired mental function was associated with impaired or delayed growth in 20% of subjects, though growth retardation alone is rare (4%) (Dumitrescu and Refetoff, 2013b; Grasberger et al., 2005).

The relationships between thyroid and cognitive and emotional dysfunctions are complex. It has been reported that patients with subclinical hypothyroidism often display a comorbidity with major depression (Howland, 1993; Prange, 1996; Bauer, 2002; Bauer et al., 2005). In keeping with this notion we have recently demonstrated that postpartum alexithymia is related to lower levels of FT4 and higher levels of FT3 suggesting a pivotal role of thyroid hormones in mood regulation (Le Donne et al., 2012). In addition, there is evidence that thyroid dysfunction increases the risk of dementia (Kapaki et al., 2003; Stern et al., 2004; de Jong et al., 2006). Altogether, these findings suggest that thyroid hormones might have a profound influence on neurotransmission and synaptic activity in cortical circuits involved in cognitive and emotional regulation (Dratman and Gordon, 1996; Gordon et al., 1999).

Despite the evidence that thyroid hormones affect brain function in adults, the underlying molecular mechanisms remain poorly understood (Calza et al., 1997). It is known that thyroid hormones action is mediated by nuclear receptors that are widely distributed throughout the brain and influences several neurotransmitters (serotonin, norepinephrine, GABA and glutamate) (Bauer et al., 2003). Furthermore, studies in rodents showed that hypothyroidism

disrupts inhibitory and excitatory neurotransmission, synaptic plasticity, learning and memory (Calza et al., 1997; Vara et al., 2003; Alzoubi et al., 2005).

Transcranial magnetic stimulation (TMS) is a non invasive technique of great value to investigate cortical physiology. Single and paired-pulse TMS studies have been used to characterize several motor cortex excitability measures and the putative inhibitory and excitatory neurotransmitters which modulate them. These parameters have been employed in several neurological and psychiatric diseases in order to elucidate the underlying neurochemical dysfunctions (Ziemann et al., 1998). In a previous TMS-based study (Rizzo et al., 2008), we demonstrated that primary overt hypothyroidism (OH) affects cortical excitability, influencing both inhibitory and excitatory intracortical circuitries. Indeed, we found a decrease of cortical excitability that paralleled an impairment of inhibitory cortical circuits. Cortical excitability was normalized when the L-thyroxine replacement therapy restored euthyroidism (Rizzo et al., 2008).

Aim of the present TMS-based study was to determine whether RTH affects cortical excitability and modulates inhibitory and excitatory intracortical circuits. For this aim, we investigated patients with RTH, patients with OH and euthyroid subjects.

Materials and Methods

Subjects

We selected four RTH patients, 1 male and 3 females, with a mean age of 20.5 years range 8-32 without any ADHD features (see Table 1). All had frankly increased serum FT3 and FT4, with inappropriately unsuppressed serum TSH. In two patients, serum TSH was even slightly above normal. The presence of goiter (as a result of the action of unsuppressed TSH on thyroid tissue) and tachycardia (as a result of the spill-over of the increased thyroid hormones on the normally functioning TR α , which are relatively abundant in the heart) (see Table 1) completed the evident picture of the RTH syndrome in these 4 patients. As expected, variable was the pattern of refractoriness (or responsiveness) of peripheral tissues (liver, bone, skeletal muscles), as measured by serum levels of certain markers (Dumitrescu and Refetoff, 2013b).

Index	A	B	C	D	Reference range for serum levels
Sex	female	male	female	female	
Age at observation (years)	32	8	15	27	
Clinical findings					
Goiter	yes	yes	yes	yes	
Heart rate (beats/min)	106	95	88	90	
ADHD	No	No	No	No	
Pituitary/thyroid axis					
Serum FT3 (pmol/L)	13.4	11.1	13.6	10.2	3.3 - 6.9
FT4 (pmol/L)	37.3	43.0	50.5	35.7	12 - 22
TSH (mU/L)	4.5	2.3	3.3	5.0	0.27 - 4.2
Serum concentration of peripheral indices of thyroid hormone action					
Serum SHBG (nmol/L)	46.6	29	45	51	20-85 (F), 9-55 (M)
Ferritin (pmol/L)	139	248	410	319	22-650 (F), 30-760 (M)
Osteocalcin (µg/L)	39	71	153	20	15-145 (F & M, children/adolescents) 7.7 - 31.9 (F > 20 yrs) 11-37 (M >20 yrs)
ALP (U/L)	88	66	103	94	40 - 270
CPK (U/L)	74	12	79	85	32 - 200
Total cholesterol (mmol/L)	5.4	4.3	3.8	3.7	3.3 - 5.2
Triglycerides (mmol/L)	1.9	0.7	1.2	1.3	0.6 - 1.9

* Physiologically, serum SHBG, ferritin, osteocalcin and ALP are up-regulated by thyroid hormones, while CPK and lipids (cholesterol and triglycerides) are down-regulated. Thus, for instance, in case A the increase in serum osteocalcin is appropriate for the high levels of circulating thyroid hormones, but the increase in serum total cholesterol and the borderline increase in serum tryglycerides are not.
 § Abbreviations, in alphabetical order: ADHD = attention deficit hyperactivity disorder; ALP = alkaline phosphatase; CPK = creatine phosphokinase; FT3 = free triiodothyronine; FT4 = free thyroxine, SHBG = sex-hormone binding globulin; TSH = thyrotropin

At molecular level, patient A was heterozygous for a mutation at nucleotide 1249 (exon 9) of the TR β gene resulting in a D322N change in the gene product. Patient B was the son of patient A, and shared her heterozygous mutation. Patient C was heterozygous for a mutation at nucleotide 1614 (exon 10) of the TR β gene resulting in a K443N change in the gene. Patient D was heterozygous for a mutation at nucleotide 1282 (exon 9) of the TR β gene resulting in a E333Q change in the gene product.

As controls for the 4 RTH patients, we used two groups of subjects: patients with OH and healthy euthyroid individuals. To be included, the controls and OH patients fulfilled the following inclusion criteria: a) normal neurological examination (except

for obvious alteration, such as delayed tendon reflexes, in OH patients), and normal brain nuclear magnetic resonance; b) normal Mini-Mental State Exam (MMSE score); c) negative history for depression, as ruled out with the Montgomery-Asberg Depression Rating Scale (MADRS), and negative history for other psychiatric illnesses; d) no treatment with cholinesterase inhibitor or with drugs interfering with cerebral cortex excitability, such as antidepressants, benzodiazepines and neuroleptics in the 30 days before the study.

OH patients (4 men, 6 women; age 53±8 years) consisted of 9 patients with autoimmune hypothyroidism due to Hashimoto's thyroiditis and one patient with iatrogenic hypothyroidism due to radioiodine therapy as a radical therapy for

hyperthyroidism. Their biochemical picture was: TSH= 24.2 ± 5.0 mU/L, FT3= 2.9 ± 0.35 pmol/L, and FT4= 7.7 ± 1.71 pmol/l. The biochemical picture of euthyroid individuals (4 men, 6 women; age 48 ± 11 years was: serum TSH= 1.86 ± 0.45 mU/L, FT3= 4.205 ± 0.15 pmol/L, and FT4= 16.32 ± 0.35 pmol/L. The protocol was approved by the local Ethics Committee in accordance with the Declaration of Helsinki on the use of human subjects in experiments. All subjects included in the study gave a written informed consent.

TMS stimulation and recording protocol

TMS was performed with a standard figure-of-eight shaped coil connected to a Magstim Rapid stimulator (Magstim Company, Whitland, Dyfed, UK). The mean loop diameters of the coil were 9 cm. The magnetic stimulus has a monophasic waveform with a pulse width of approximately 300 μ s. The junction region of the coil points backwards and laterally at a 45° angle away from the midline, approximately perpendicular to the line of the central sulcus. The coil was placed tangentially to the scalp at the optimum scalp position which consistently elicited the largest motor evoked potentials (MEPs) with the steepest slope in the right first dorsal interosseus (FDI) muscle ("motor hot spot").

Recording system

EMG was recorded from Ag-AgCl surface electrodes over the right FDI muscle using a belly-tendon montage. The signal was amplified and bandpass filtered (32 Hz to 1 KHz) by a DIGITIMER D 150 amplifier (Digitimer Ltd., Welwyn Garden City, Herts, UK) and stored at a sampling rate of 10 KHz on a personal computer for off-line analysis (SigAvg Software, Cambridge Electronic Design, Cambridge, UK). During the experiments EMG activity was continuously monitored with visual (oscilloscope) and auditory (speakers) feedback. Trials in which the target will be not relaxed were discarded from analysis.

Measures of cortical excitability

Changes in motor cortical excitability were probed using single-pulse TMS and a paired-pulse approach. Monophasic pulses were given to the left motor

cortex using a high-power Magstim 200 stimulator (Magstim, Whitland, Dyfed) and a standard figure-of-eight coil, with external loop diameters of 9 cm. The centre of the coil was located over the "motor hot spot" for stimulation of the contralateral FDI muscle and the handle of the coil pointed 45° postero-laterally. The monophasic magnetic stimulus had a rise time of approximately 100 μ s, decaying back to zero over approximately 0.8 ms. The coil current during the rising phase of the magnetic field flowed toward the handle. Thus, the induced current in the cortex flowed in a postero-anterior direction.

We assessed several measures of cortical excitability including resting motor threshold (RMT), motorevoked potentials (MEPs) input-output recruitment curve at stimulus intensities ranging from 100% to 150% RMT, cortical silent period (CSP), and short interval cortical inhibition (SICI) and intracortical facilitation (ICF).

RMT was defined as the minimum intensity that could evoke a peak-to-peak MEP of 50 mV in at least 5 out of 10 consecutive trials in the relaxed FDI muscle. MEPs Input-Output recruitment curve was performed at stimulus intensities ranging from 100% to 150% RMT (in steps of 10%). 10 peak-to-peak MEP at each stimulation intensities were averaged. Cortical Silent Period (CSP) was recorded at stimulus intensities of 130% RMT during isometric voluntary contraction (30% of maximum effort) of the right FDI muscle, using a strain gauge.

CSP duration was defined in the single trials from the time of the magnetic stimulus to the first reoccurrence of a continuous voluntary EMG activity. For CSP measurements, ten consecutive MEPs were rectified but not averaged.

Short interval cortical inhibition (SICI) and intracortical facilitation (ICF), were determined by using a conditioning-test paradigm (Kujirai et al., 1993). Briefly, the intensity of the conditioning stimulus was set at 90% RMT. The intensity of the test stimulus was adjusted in order to have a MEP of about 1 mV amplitude. We studied two different inter-stimulus time intervals (ISI). A single block of 30 trials of 10 control trials (test alone) and 20 paired stimulation trials (10 for each condition) was performed. For each ISI, the amplitude ratio of the mean conditioned MEP to the control MEP was determined. SICI and ICF were defined as the averages of the MEP ratios obtained at inhibitory ISI of 2 ms and facilitatory ISI of 12 ms, respectively.

Table II. - Mean values and standard errors of all cortical measures

	CONTROLS	RTH	OH
RMT (FDI) %	44±6	44±12	47.9±4.9
MEP mV FDI 100% RMT	0.13±0.001	0.04±0.02	0.09±0.02
MEP mV FDI 110% RMT	0.43±0.01	0.33±0.2	0.07±0.01
MEP mV FDI 120% RMT	0.9±0.02	0.7±0.2	0.4±0.1
MEP mV FDI 130% RMT	2.1±0.14	1.1±0.2	0.5±0.12
MEP mV FDI 140% RMT	2.5±0.14	1.7±0.5	0.9±0.2
MEP mV FDI 150% RMT	3.0±0.1	1.9±0.6	1.1±0.2
SICI mV FDI	0.4±0.01	0.13±0.04	0.7±0.04
ICF mV FDI	1.3±0.06	0.9±0.1	1.4±0.06
CSP msec FDI	157±1.2	107±7.4	182±5.2

Statistical analysis

Factorial ANOVA was employed to show differences in RMT, CSP, SICI and ICF between patients and controls. MEP recruitment curves in patients and controls were evaluated in separate repeated-measures analyses of variance (ANOVA). We computed a two-way repeated measures ANOVA with intensity (6 levels: 100, 110, 120, 130, 140, 150% of MT) as within-subject factor and group (3 levels: OH patients, RTH patients and controls) as between subjects factor. If appropriate, *post hoc* t tests were performed. Significance was set at $p<0.05$. Data are given as mean \pm standard error of the mean.

Results

The relevant data of RTH patients are summarized in Table 1. TMS caused no complains in either patients or controls. The mean values and the standard errors of all cortical measures (RMT, MEP IO-CURVE, SICI and CSP) are reported in Table 2.

Motor threshold

At baseline, RMT was 44 ± 6 in controls, 47.9 ± 4.9 in OH patients, and 44 ± 12 in RTH patients. Compared to controls, RMT was significantly higher in the OH patients ($F=6.5$, $p=0.019$), whereas it was similar in RTH patients ($F=0.22$, $p=0.8$).

MEP recruitment curves

As shown in Fig. 1, MEP amplitudes increased with increasing stimulus intensity in controls and both OH and RTH patients. However, MEP recruitment

curve was significantly less steep in OH patients compared to RTH patients and controls. Repeated ANOVA indicated a significant effect for intensity ($F=34.8$, $p < 0.001$) with a significant interaction between intensity and groups ($F=4.36$, $p = < 0.001$). Indeed *post hoc* analysis showed that MEP amplitudes were significantly lower in OH patients compared to either controls ($t = 4.91$, $p = < 0.001$) or RTH patients ($t = -2.38$, $p = 0.02$). On the contrary, in RTH patients MEPs amplitudes were slightly different from controls ($t = 1.78$, $p = 0.07$).

Inhibitory and facilitatory parameters

The duration of CSP was different in both OH and RTH patients compared with controls ($F=36.4$; $p < 0.001$). *Post hoc* analysis showed that CSP was significantly longer in OH compared with controls ($t = -3.67$; $p = 0.0017$) and RTH patients ($t = 7.72$, $p < 0.001$). On the other hand, CSP was significantly shorter in RTH patients compared with controls ($t = 6.48$, $p < 0.001$) (Fig.2). Another parameter of cortical inhibition, SICI, was different in patients compared to controls ($F=34.03$; $p < 0.001$). *Post hoc* analysis showed again that SICI was reduced in OH patients compared to controls ($t = -5.62$, $p < 0.001$) and RTH patients ($t = 6.90$, $p < 0.001$), while it was significantly increased in patients with RTH compared to controls ($t = 3.84$, $p = 0.005$). (Fig.3) We then assessed the facilitatory intracortical mechanisms evaluating ICF. We found that there was a borderline difference between controls and RTH patients ($t = 3.11$, $p = 0.08$) or OH patients ($t = 3.40$, $p = 0.05$), suggesting that thyroid dysfunction has not a massive effect on intra-cortical facilitatory circuits.

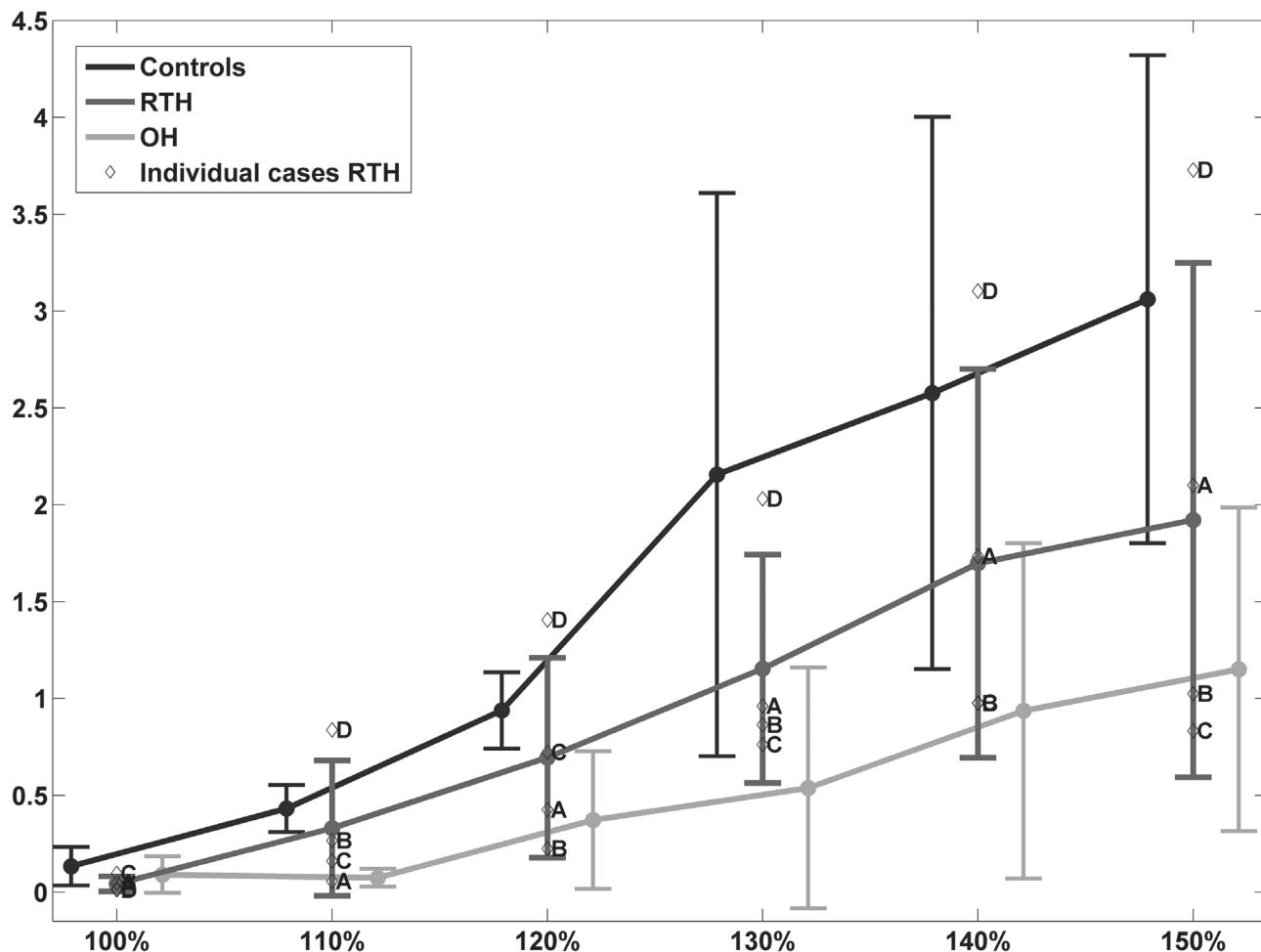


Fig. 1. - Effects of thyroid hormone dysfunction on motor evoked potential (MEP) recruitment curve (IO-curve). MEP amplitudes increased with increasing stimulus intensity in the four patients with RTH (cases A, B, C, D), 10 patients with overt OH and 10 euthyroid controls. However, MEP amplitudes were significantly lower in OH patients compared to either controls ($p = < 0.001$) or RTH patients ($p = 0.02$).

Discussion

Our results demonstrate that dysfunction of thyroid hormones (THs) may influence both excitatory and inhibitory cortical mechanisms. Indeed, in line with our previous work (Rizzo et al., 2008), we showed a decrease of cortical excitability in OH, as indicated by the increased motor threshold and by the abnormal recruitment curve. A new finding was that in both RTH and OH patients the inhibitory cortical circuits were impaired as well, and the abnormalities that we found were opposite in the two class of patients. In OH patients we found a prolongation of the cortical silent period (CSP) and a reduction of the short interval intra-cortical inhibition (SICI). On the contrary, RTH patients showed a reduction of CSP

associated with and increasing of SICI. These results confirm that thyroid hormones modulate cortical excitability. It is likely that the increase in RMT in OH patients could be due to cortical changes in Na^+ channels activity, which are related to the regulation of Na^+ concentration at a cellular level induced by THs and to modulation of the cellular Ca^+ homeostasis (Garcia and Strehler, 1999; Zylinska and Soszynski, 2000; Acharya and Katyare, 2005; Rizzo et al., 2008).

In our previous report (Rizzo et al., 2008), we found that the steepness of the recruitment curve was reduced in OH patients compared to controls. We interpreted this finding as the result of the action of THs to adrenergic, glutamatergic and serotonergic neurotransmission (Bauer, 2002; Ilic et al., 2002; Plewnia et al., 2002; Bauer et al., 2003; Bauer et al.,

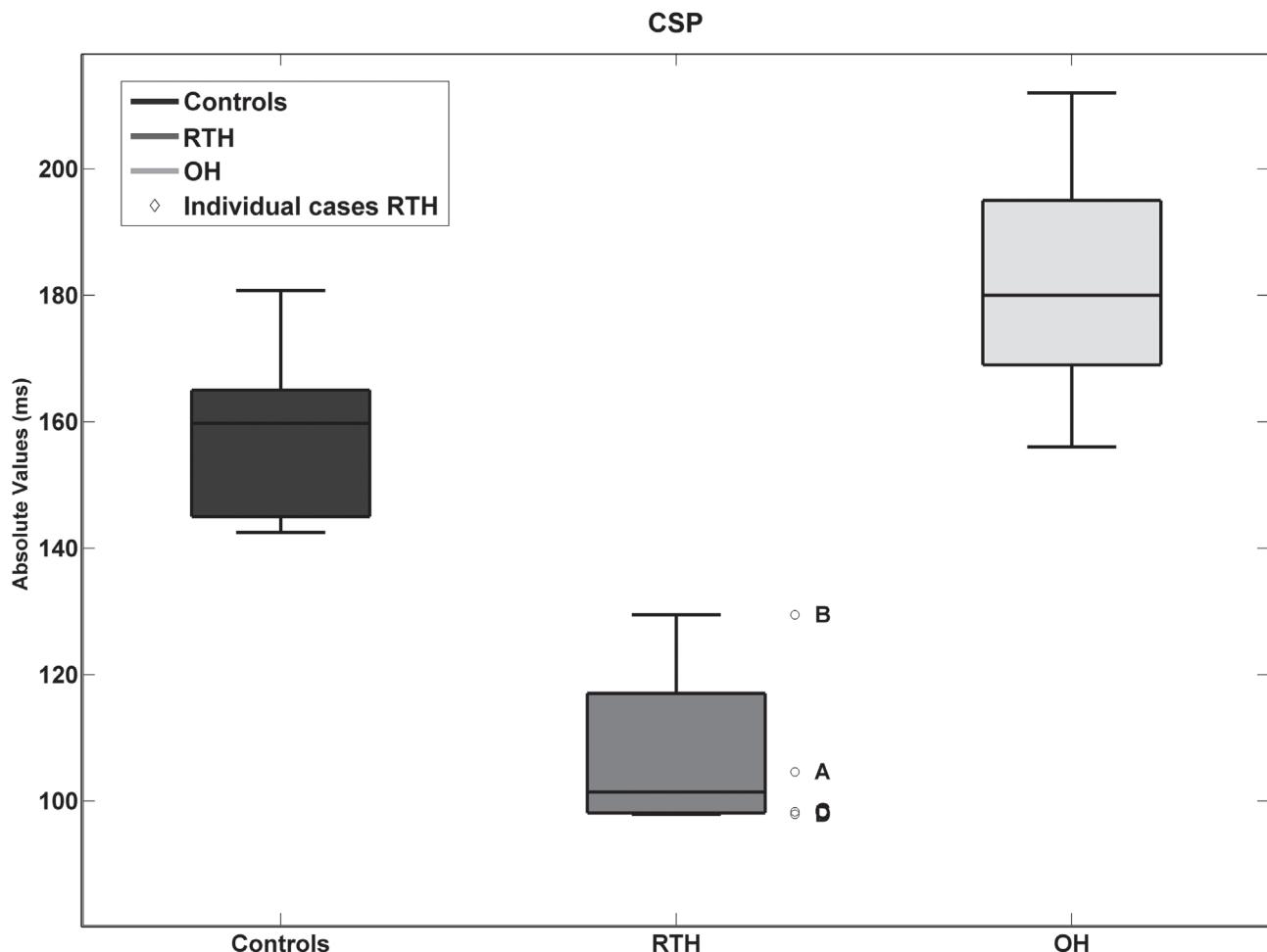


Fig. 2. - Effects of thyroid hormone dysfunction on cortical silent period (CSP). CSP was significantly longer in OH compared with controls ($p = 0.0017$) and RTH patients ($p < 0.001$). On the other hand, CSP was significantly shorter in RTH patients compared with controls ($p < 0.001$).

2005; Losi et al., 2008). Interestingly the recruitment curve was steeper in RTH compared to OH patients. Hence, the increased slope of the recruitment curve could be explained by the opposite concentration of thyroid hormones in the blood and brain of RTH patients vs OH patients.

Another important finding was the abnormality of CSP and SICI in both RTH and OH patients. The abnormality could be explained by the reported effect of thyroid hormones in the regulation of GABA's metabolism, release, reuptake and receptors expression (Sandrini et al., 1993; Gadea and Lopez-Colome, 2001). Again, the fact that in RTH patients the dysfunctions in CSP and SICI are opposite compared to OH patients are probably related to the opposite concentrations of THs in the blood and brain of RTH patients vs OH patients.

Thyroid hormones are of primary importance for the perinatal development and normal function of the central nervous system. These hormones primarily regulate the transcription of specific target genes, increase the cortical serotonergic neurotransmission, and play an important role in regulating central noradrenergic and GABA function. Thyroid deficiency during the perinatal period results in mental retardation. Hypothyroidism of the adults causes most frequently dementia and depression and increases predisposition to stroke. Nearly all the hyperthyroid patients show minor psychiatric signs, and infrequently psychosis, dementia, confusion state, depression, apathetic thyrotoxicosis, thyrotoxic crisis, seizures, pyramidal signs, or chorea occur (Aszalos, 2007).

A common behavioural phenotype associated with RTH is attention deficit hyperactivity disorder

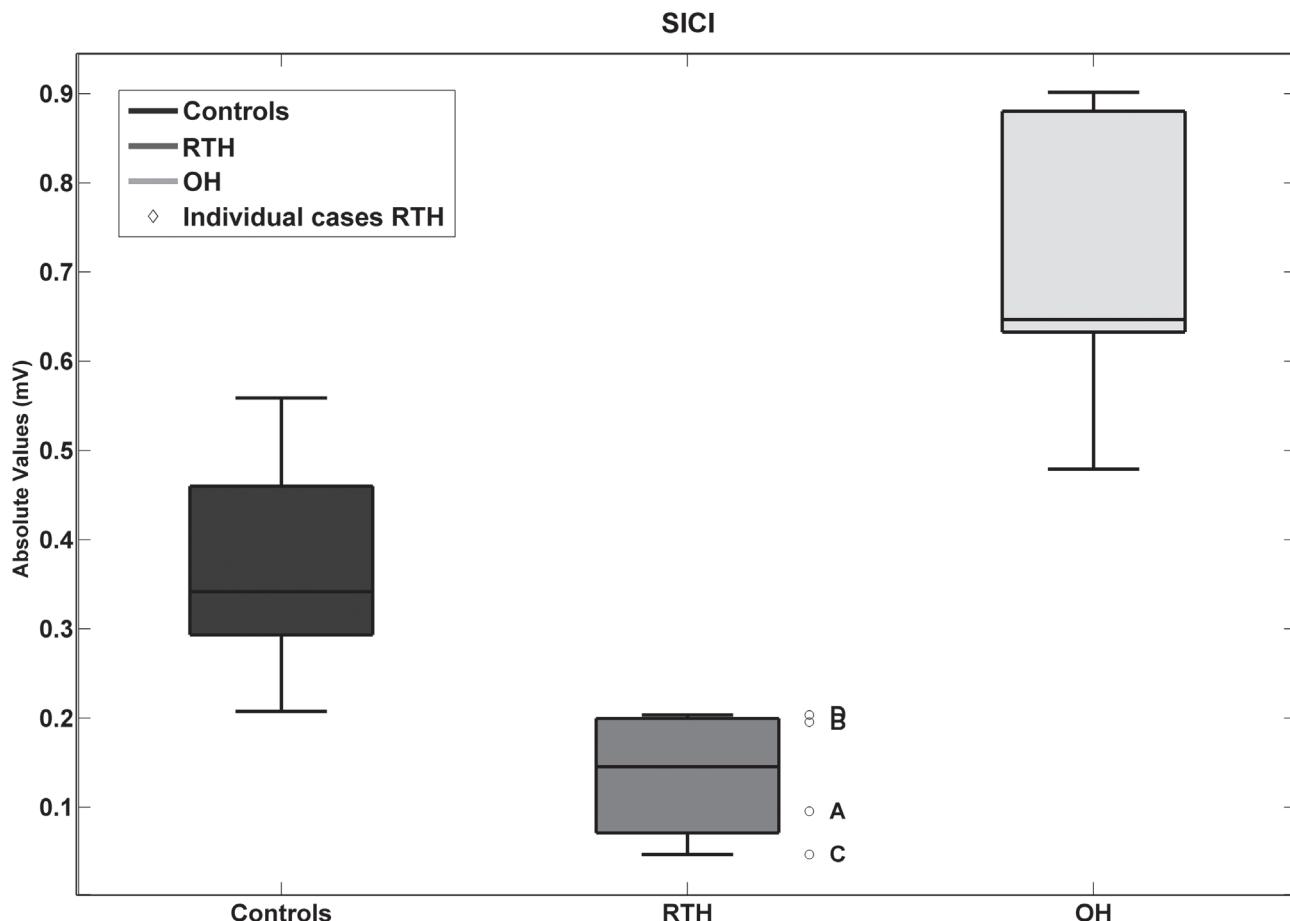


Fig. 3. - Effects of thyroid hormone dysfunction on Short interval cortical inhibition (SICI). SICI was reduced in OH patients compared to controls ($p < 0.001$) and RTH patients ($p < 0.001$), while it was significantly increased in patients with RTH compared to controls ($p = 0.005$).

(ADHD) (Dumitrescu and Refetoff, 2013b; Hauser et al., 1993). In previous studies, SICI was found significantly reduced in children with ADHD and there was a strong correlation between SICI and symptom severity (Moll et al., 2000; Gilbert et al., 2011). Interestingly, none of our RTH patients showed any clinical features of ADHD. We might speculate that a greater amount of SICI could prevent the occurrence of ADHD.

In conclusion, we demonstrated that conditions that share some clinical features such as RTH and OH, but with opposite levels of thyroid hormones, are associated with opposite abnormalities in cortical excitability. Our findings may set the stage for future research on thyroid dysfunction (including hyperthyroidism), to better understand the role of thyroid hormones in regulating cortical excitability and to try to recognize the relationship between these hormones and mood or cognitive functions.

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