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Neural response to transcranial magnetic stimulation in adult hypothyroidism and effect of replacement treatment

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Abstract

Purpose: Despite clinical evidences that hypothyroidism is often associated with cognitive dysfunction, affective disorders and psychosis, the effects of thyroid hormone deficiency on the adult brain have been largely unexplored. We investigated the hypothesis that hypothyroidism might affect cortical excitability and modulates inhibitory and excitatory cortical circuits by using Transcranial Magnetic Stimulation.
Materials and methods: Cortical excitability was probed in 10 patients with overt hypothyroidism and 10 age-matched healthy controls. We tested motor thresholds and corticospinal excitability, cortical silent period and peripheral silent period, short interval intracortical inhibition, intracortical facilitation. Patients were evaluated at the time of diagnosis, as well as after 3 and 6 months replacement therapy with L-thyroxin.
Results: At baseline, patients showed decreased cortical excitability, with increased resting and active motor threshold and decreased steepness of the motor evoked potential recruitment curves. These changes were paralleled by longer cortical silent period and decreased short interval intracortical inhibition. After 3 months replacement therapy, all the parameters but short interval intracortical inhibition were restored to normal values. Short interval intracortical inhibition returned to normal values only after 6 months of replacement therapy.
Conclusions: Thyroid hormones are needed to modulate cortical excitability and cortical inhibitory circuits in adults.

Keywords: TMS; Hypothyroidism; Cortical excitability

1. Introduction

Thyroid hormones (THs) are key regulators of metabolism and development and are known to have pleiotropic effects in many different organs including the central nervous system [1]. Their importance for the normal function of the adult brain is substantiated by the frequent association of thyroid dysfunctions with the presence of neurological and psychiatric symptoms. In particular, neuropsychological and affective alterations, such as depression, anxiety, progressive cognitive impairment and memory loss, are often present in both subclinical and overt hypothyroidism

Abbreviations: OH, overt hypothyroidism; TMS, transcranial magnetic stimulation; TH, thyroid hormones; MEP, motor evoked potential; CSP, cortical silent period; PSP, peripheral silent period; SICI, short interval intracortical inhibition; ICF, intracortical facilitation.

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(OH) [2,3]. These symptoms are paralleled by decreased cerebral blood flow in regions involved in the regulation of attention, mood, motor functions, memory and visuo-spatial processing [4].

The relationships between hypothyroidism and cognitive and emotional dysfunctions are complex. It has been reported that patients with subclinical hypothyroidism often display co-morbid major depression and THs have been used both to augment and accelerate the clinical effects of antidepressants [5–8]. In addition, there is evidence that thyroid dysfunction increases the risk of dementia [9–11]. Altogether, these findings suggest that THs might have a profound influence on neurotransmission and synaptic activity in cortical circuits involved in cognitive and emotional regulation [12,13].

Despite the evidence that THs affect brain function in adults, the underlying molecular mechanisms remain poorly understood [14]. It is known that THs action is mediated by nuclear receptors that are widely distributed throughout the brain and influences several neurotransmitters (serotonin, norepinephrine, GABA and glutamate) [15]. Furthermore, studies in rodents showed that hypothyroidism disrupts inhibitory and excitatory neurotransmission , synaptic plasticity and learning and memory [16,17,14].However, these results need to be confirmed in hypothyroid patients.

Transcranial magnetic stimulation (TMS) is a non-invasive technique valuable 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 [18].

Thus, in this study we determined whether OH affects cortical excitability and modulates inhibitory and excitatory intracortical circuitries by using TMS. Given that cognitive and affective abnormalities that accompany hypothyroidism are reversed once euthyroidism is restored, we also investigated whether hormone-replacement treatment can restore physiologic cortical excitability.

2. Methods

2.1. Subjects

Subjects were 10 patients with OH (4 men, 6 women, age: mean±SD 53±8 years) referred to the Endocrinology Unit, University of Messina, Italy, and ten age- and gender-matched normal controls. OH was diagnosed on the basis of elevated serum TSH levels (>4.5 mIU/L (mU/L) and lowered free thyroxine (T4) levels (<12 pmol/L). The causes of OH included Hashimoto's thyroiditis ($n=9$) and radioiodine therapy ($n=1$) for hyperthyroidism treatment. Patients underwent a complete neurological examination and brain MRI and fulfilled the following inclusion criteria: 1) Negative history for depression (score <16 Montgomery–Asberg Depression Rating Scale-MADRS), peripheral neuropathy and myopathy (normal EMG examination); 2) normal Mini-Mental State Exam (MMSE; score >27) [19]; 3) No treatment with psychoactive drugs with psychoactive drugs; 4)negative history for vascular dementia, stroke, epilepsy, convulsions.

Controls were 10 age-matched healthy caregivers. All patients and controls were right-handed according to the Edinburgh Handness Inventory and gave their informed consent for the study, which was approved by the Institutional Ethics Committee. Patients underwent TMS and laboratory testing at the time of diagnosis (baseline) as well as at the end the third and sixth month of replacement therapy with L-thyroxin (range 75–150 μg/die). Control subjects were tested only at baseline.

2.2. Laboratory investigation

TSH and THs were determined in serum samples that were stored at −20 °C until assay. For the purpose of this investigation, each hormone in all 40 sera was assayed in a single run. Serum TSH, fT3 and fT4 are summarized in Table 1.

2.3. TMS stimulation and EMG recordings

Patients and controls underwent a series of tests with TMS. All subjects were seated in a comfortable reclining chair and surface EMG was recorded from the right first dorsal interosseus (FDI) muscle using disposable disc electrodes with a belly-tendon montage. EMG was filtered by Neurolog System supplied by Digitimer with a time constant of 3 ms, and a high pass filter set a 3 kHz. TMS was performed using a Magstim 200 HP magnetic stimulator (Magstim, Whitland, UK), which was connected to one figure of 8 shaped coil. Signals were collected via a CED 1401 laboratory interface (Cambridge Electronic Design, Cambridge, UK) and fed to a personal computer for offline analysis. Stimulation and recording procedures are described in details elsewhere [20–23]. We studied several parameters of cortical excitability including:

1) Resting motor threshold (RMT), defined as the minimal stimulus intensity required to produce MEPs>50 μV in at least 5 out of 10 consecutive trials;
2) Active motor threshold (AMT), defined as the minimum intensity necessary to induce a MEP of at least 200 μV in

Table 1
Thyroid function tests in patients with hypothyroidism at baseline, after 3 and 6 months of replacement therapy

	TSH levels (mU/L)	FT3 levels (pmol/L)	FT4 levels (pmol/L)
Controls	1.86±0.45	4.205±0.15	16.32±0.35
Hypothyroid	24.23±4.98	2.9±0.35	7.72±1.71
Replacement 3 months	2.16±0.35	3.720±0.29	17.07±0.63
Replacement 6 months	1.42±0.51	4.015±0.25	18.21±0.36