



Research of the Effect of Hyperthyroidism on Reaction Time Using the Oddball Paradigm

Hipertiroidilerde Reaksiyon Zamanının Oddball Paradigması ile Araştırılması

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ABSTRACT

Aim: Thyroid hormones are so important for the normal physiological functions and the cognitive functions of brain. It is known that hyperthyroidism, the presence of excessive thyroid hormone produced by the thyroid gland, causes changes in cognitive functions. In this study, we have examined the effect of hyperthyroidism on motor response that result from this cognitive process by measuring reaction time to auditory stimuli.

Material and Method: The study was conducted on newly diagnosed hyperthyroid patients (n=20) and healthy controls (n=20). The reaction time was evaluated in an auditory oddball paradigm. For that purpose, participants have been listened to 160 sound stimuli (120 standards, 40 targets). We asked them to press the button under their right hand when they hear the target sounds. The elapsed time between the presentation of the stimulus and the subsequent pressing button has been defined as reaction time.

Results: Reaction time was significantly prolonged in the hyperthyroid group compared with the control group ($p \leq 0.001$).

Conclusion: Hyperthyroid patients had prolonged perception time and significant decrease on attention and concentration. They can be result in prolonged reaction time because of impaired motor functions.

Key words: hyperthyroidism; Oddball paradigm; reaction time; human; cognition

ÖZET

Amaç: Tiroid hormonları beyinde fizyolojik ve bilişsel işlevler için oldukça önemlidir. Tiroid bezinden aşırı tiroid hormonu üretimi ile karakterize olan hipertiroidizmin bilişsel işlevlerde değişikliklere neden olduğu bilinmektedir. Bu çalışmada, işitsel uyarılara reaksiyon zamanı ölçülerek hipertiroidi'nin bilişsel süreçten kaynaklanan motor yanıt üzerine etkisi araştırıldı.

Materyal ve Metot: Çalışma, yeni tanı konmuş hipertiroidi hastaları (n=20) ve sağlıklı kontrol grubu (n=20) üzerinde yürütüldü. Tepki süresi işitsel oddball paradigması ile değerlendirildi. Bu amaçla katılımcılara 160 ses uyarısı verildi (120 standart, 40 hedef). Katılımcılara ses uyarısını duyduklarında sağ ellerinin altındaki butona basmalarını istendi. Uyarının verilmesi ve butona basma süresi arasında geçen süre reaksiyon zamanı olarak hesaplandı.

Bulgular: Reaksiyon zamanı anlamlı şekilde hipertiroidi grubunda kontrol grubuna göre uzadı ($p \leq 0,001$).

Sonuç: Hipertiroidili hastalarının algılama süreleri uzamakta, dikkat ve konsantrasyonda anlamlı azalma olmuştur. Bu duruma bozulmuş motor fonksiyondan kaynaklanan uzamış reaksiyon zamanı neden olmuş olabilir.

Anahtar kelimeler: reaksiyon zamanı; Oddball paradigması; hipertiroidi; insan; biliş

Introduction

Thyroid hormones are critical regulatory molecules which are quite important for the mammal physiology with their functions such as the development of fetal and post-natal nervous system, the maintenance of adult brain functions, as well as the development and organ functions¹. In addition to memory, cognitive and motor functions; thyroid hormones are closely related with numerous pathophysiologic conditions such as subfertility, mood disorders, depression and dementia^{2,3}. Although there are numerous studies examining the effects of thyroid hormones on cognitive dysfunction and psychiatric symptoms, the primary processes underlying these disorder have not exactly been clarified yet^{4,5}. These primary processes probably appear as a complex result of the effects of thyroid dysfunction on the cellular metabolic processes and its primary and secondary effects on the neural networks⁶.

Hyperthyroidism is an illness diagnosed with clinically decreased amount of thyroid stimulating hormone (TSH) and/or increased serum triiodothyronine (T3) and thyroxine (T4) levels⁷. Low or high TSH concentrations (within the reference range) and low cognitive performance have been associated^{8,9}. Hyperthyroid causes increased resting energy consumption, loss of weight, decreased cholesterol levels, increased lipolysis, and development of hypermetabolic conditions characterized by gluconeogenesis^{10,11}. The studies have revealed that hyperthyroidism leads to cognitive dysfunctions, the development of bipolar disorders and changes in brain size^{12,13}. The studies have also indicated that excessive thyroxine causes the oxidative stress and damage on neurons¹⁴. Among the patients with Graves, which is a type of hyperthyroidism illness, cognitive disorders have been observed in the toxic phase of thyrotoxicosis, but no cognitive disorders have been found in the neuropsychological tests¹⁵. Wijsman et al., determined no correlation regarding cognitive dysfunction among the elderly patients having hypo or hyperthyroid with no clinical characteristics¹⁶.

In the studies, it was seen that the temporary profound hypothyroid was characterized by reversible depression and it caused fine motor performance, reaction time and process rate to decrease¹⁷. Therefore, the aim of this study was to measure the reaction time in hyperthyroid patients and to investigate on whether they caused dysfunction in cognitive and motor functions through oddball paradigm.

Material and Method

Patient Selection

The study was performed in the Electrophysiology Laboratory of the Department of Physiology, Faculty of Medicine in Erciyes University. Patients having hyperthyroid disease were randomly enrolled in the study protocol. Randomization was carried by enrolling patients consecutively as they were referred to the endocrinology clinic at Erciyes University Hospital. Age and sex matched volunteers were taken as controls. The control group was healthy volunteers without no clinical evidence of thyroid dysfunction. The study was conducted on 20 newly diagnosed hyperthyroid female and male patients with mean age of 39.6 ± 1.8 years and 20 healthy individuals as control group with mean age of 42.2 ± 2.0 years. The hyperthyroid patients were diagnosed with general history, clinical examination and serum levels of fT3, fT4 and TSH. The patients were belonged to

middle socioeconomic status. Intelligence was not evaluated in this study, but all participants had completed high school. They also had hyperthyroid symptoms. The average interval between the diagnosis and start of symptoms was about 6–12 months. The subjects were categorized into 2 groups: group I=healthy controls; group II=hyperthyroid patients. All participants of the study gave informed consent to participate in accordance with the Helsinki declaration. All experiments were performed according to the guidelines of the Erciyes University Ethics Committee (08/236). Subjects suffering from any hearing impairment, systemic disease or any history of drug abuse (nicotine, alcohol, opium etc.) and pregnant women were excluded from the study.

Determination of Reaction Time

The reaction time was evaluated in an auditory oddball paradigm. For that purpose, participants have been listened to 160 sound stimuli (120 standards, 40 targets). We asked them to press the button under their right hand when they heard the target sounds. The elapsed time between the presentation of the stimulus and the subsequent pressing button has been defined as reaction time.

Correct response times to target stimuli were calculated Standard (2000 Hz) and target (1500 Hz) auditory stimuli were presented binaurally over headphones to the subject with duration of 1000 msec. The target tone occurred regularly with a 0.20 probability. The rise and fall time of each tone was 5 msec¹⁸.

The obtained data was analyzed by using SPSS software (version 13.0). The data is expressed as mean \pm standard deviation (SD). The statistical analysis for the comparison between control group and hyperthyroid patients for the thyroid hormone were done using ANOVA and reaction time Mann Whitney U. Differences were considered significant when $p < 0.05$.

Results

Presence of a neurological or psychiatric disorder (especially, the taking of neuropsychiatric medications), another metabolic and endocrine disorder, malignancy and pregnancy were determined as the exclusion criteria for all participants (especially, the taking of neuropsychiatric medications). No statistically significant difference was found on the comparison of groups based on age ($p > 0.05$). On the other hand, in the comparison of hormone values, serum sT3 and sT4 levels of hyperthyroid patients were found to be higher than the control group ($p = 0.001$). In patients with hyperthyroid and

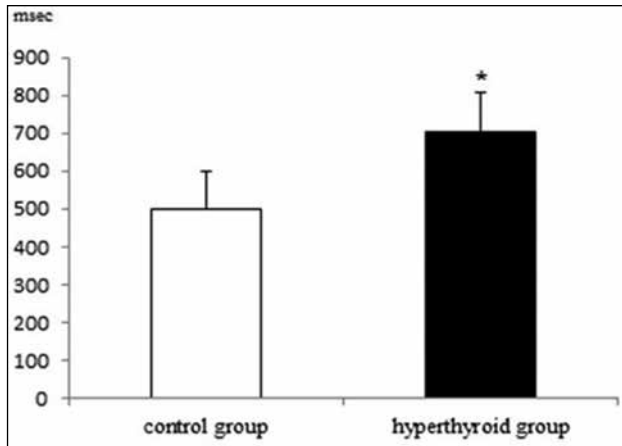


Figure 1. Comparison of reaction time determined by oddball paradigm between groups.

control groups, the hormone levels were respectively 4.38 ± 0.2 and 3.13 ± 0.07 ; ($F=14.79$) for sT_3 (pg/ml), and 16.49 ± 1.0 and 8.19 ± 0.21 ; ($F=43.75$) for sT_4 (pg/ml). The TSH ($\mu\text{u/ml}$) hormone was found as 0.05 ± 0.2 among the hyperthyroid group, and 2.6 ± 0.1 ($F=111.01$, $p=0.001$) in the control group. The normal levels of hormones were taken as: sT_3 : 2.5–3.9 pg/ml sT_4 : 6.1–11.2 pg/ml, and TSH: 0.35–5.5 $\mu\text{u/ml}$, while the reaction time determined by oddball paradigm in the present study was significantly ($z=-4.46$, $p \leq 0.001$) prolonged in the hyperthyroid group (704.06 ± 104.37) compared to the control group (500.27 ± 100.92) (Fig. 1).

Discussion

Thyroid hormone plays an important role in the cognitive disorders and it is obviously detected among mood disorders, neuropsychiatric disorders, and thyroid patients⁴. Additionally, cognitive functions are a complex processes with many determinants which are not only associated with the thyroid function¹⁹. In this study, we have examined the effect of hyperthyroidism on motor response that results from this cognitive process by measuring the reaction time to auditory stimuli.

Previous studies have revealed that the hyperthyroid patients display high anxiety and less weak executive functions⁷. In their studies Yuan et al., indicated that the untreated hyperthyroid patients had a significant lack of stimulation and executive function networks²⁰. Again, when hyperthyroid patients were compared with thyroid patients, it was found that there was a significant decrease in attention, concentration, verbal

memory and executive functions²¹. In these studies, the remarkable finding was that in addition to the other dysfunctions on the neural network functions, the decrease in the executive functions was a common feature among hyperthyroid patients. All these studies prove hyperthyroid patients have cognitive dysfunctions. However, Vogel et al., found that there was no difference between patients with hyperthyroid, who stated that they subjectively experienced a cognitive dysfunction, in terms of their neuropsychological test performances and then when the patients were evaluated again after a year of treatment, it was observed that the symptoms significantly disappeared¹⁵.

In another study, it was found that hyperthyroid formed for a short time with the administration of 250 μg T₄ for 8 weeks caused changes in the brain structures of cerebellum with motor-sensory function related to working memory in those with hyperthyroid²². This result can be a cause for the prolonged reaction time in hyperthyroid, which we obtained in the present study; on the other hand, Gottlicher et al., revealed that following an 8-week 250 μg T₄ administration, a significant increase took place in resting-state functional magnetic resonance (fMRI), especially in rostral temporal lobe; this result was interpreted as a possible increase in the connections between temporal lobe and cognitive control network²³. Although the connections between the temporal lobe and cognitive centers increased, the reason for the prolonged reaction time was considered to be a functional insufficiency among these increased connections. In a study conducted with patients with thyrotoxicosis showing no clinical symptom, it was determined that there was no change in the declarative and working memory, and motor learning was better²⁴. In this study, however, the patients with hypothyroid were administered with T₄ and thyrotoxicosis was formed. In addition to all this information, it is known that cerebral venous diseases, cerebral aneurism, and the development of subarachnoid hemorrhage have a relationship with thyroid disorders²⁵. Again, the studies indicated that myopathy and neuromuscular weakness were observed among those with hyperthyroid^{26,27}. It was considered that as a result of these holistic effects of thyroid hormones on the nervous system, there was a prolonged reaction time of those with hyperthyroid.

The previous study showed that there was a significant increase in audio-visual reaction time in hypothyroid as well as hyperthyroid patients and auditory reaction time decreased significantly after treatment²⁸. In

another study, either in hypothyroidism or in hyperthyroidism the reaction time was considerably prolonged²⁹. The findings from these studies support the findings of our hyperthyroid patients prolonged reaction time. In conclusion, thyroid hormone is essential for the normal functioning of auditory mechanisms. Consequently, hyperthyroid patients had prolonged perception time and a significant decrease on attention and concentration. They can result in prolonged reaction time despite lack of impaired motor functions.

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