

Thyroid Hormones Role in Neuroticism Formation and Aggression Development

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Abstract

Excessive aggression has negative consequences for both individuals and society. According to some literature data, both high impulsive and premeditated aggressions are associated with high neuroticism. The association between blood serum levels of thyroid hormones and cortisol, neuroticism and physical aggression in men was studied. No correlation between thyroid hormones and physical aggression was found both in total group and in individuals with high and middle levels of neuroticism, but in persons with high neuroticism level, the involvement of thyroid hormones into prediction of physical aggression was revealed by multiple stepwise regression analysis. In men with high neuroticism level, the significant positive correlations between neuroticism and thyroxine ($r=+0.78$, $p=0.008$), between thyroxine and cortisol ($r=+0.77$, $p=0.009$) were observed, and the involvement of thyroid hormones and cortisol into prediction of physical aggression was revealed by multiple stepwise regression analysis. In men with middle neuroticism level no correlation between investigated parameters was found. Persons with high and middle levels of neuroticism didn't differ in cortisol and thyroid hormones levels, but difference in thyroxine level was almost significant (high neuroticism level – 146.72 [115.83, 169.69], middle neuroticism level 119.69 [101.67, 135.90], $p=0.079$). In men with high neuroticism level it was higher than in individuals with middle neuroticism level. Obtained data indicate the necessity of participants division depending on expression degree of personality traits to study the mechanisms of aggression development. Thyroid hormones and cortisol are involved in the formation of high level of neuroticism, which is confirmed by the results of multiple stepwise regression analysis, by the existence of significant positive correlations between neuroticism and thyroid hormones, between thyroid hormones and cortisol together with our early published data about correlation between neuroticism and cortisol in individuals with high neuroticism level. In persons with high neuroticism level, thyroid hormones are indirectly involved in aggression development due to the results of multiple stepwise regression analysis, and significant positive correlation between neuroticism and physical aggression in these individuals.

Keywords: Triiodothyronine; Thyroxine; Cortisol; Neuroticism; Aggression; Triiodothyronine (T_3); Thyroxine (T_4); Antisocial personality disorder (APD); Hypothalamic pituitary adrenal axis (HPA axis)

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Introduction

Thyroid hormones have been reported to play a role in the aggression development [1]. Excessive aggression has negative consequences for both individuals and society. Some studies indicate a correlation between serum thyroid hormone levels

and aggression and tendency to commit a crime [2,3]. In the criminal Antisocial Personality Disorder (APD) group the free triiodothyronine (T_3) level is significantly higher than in the noncriminal APD group, but no significant correlation between thyroid hormone levels and aggression is found in the criminal APD group [1]. Association between T_3 levels and violent/

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aggressive behavior is shown not only in males but also in females with borderline personality disorder [4]. According to some literature data, both high impulsive and premeditated aggressions are associated with high neuroticism [5,6].

The purpose of our research was to investigate the association between blood serum levels of thyroid hormones and cortisol, neuroticism and physical aggression in men.

Methods

Thirty-two young healthy 18- to 22-year-old male students of the Kharkiv National Medical University were enrolled in the study. All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Helsinki Declaration and later amendments or comparable ethical standards. All participants were volunteers and gave their written informed consent.

Physical aggression and neuroticism were assessed using Buss-Durkee Hostility Inventory (BDHI) and Eysenck Personality Questionnaire (EPQ), respectively. The level of physical aggressiveness was estimated relatively to a maximum possible level. The EPQ is directed toward identification of the extraversion/introversion ratio and value of the emotional stability/instability (neuroticism). In this study, we do not present the extraversion results. Neuroticism is a trait that characterizes emotional stability/instability of a person. The factor is bipolar and forms a scale. One pole of the scale includes people characterized by extreme stability and perfect adaptation (people with low level of neuroticism), and the other pole includes extremely nervous, unstable people with poor ability to adapt (people with high level of neuroticism). Most people are located between these poles, closer to the middle (people with middle level of neuroticism). The neuroticism level was assessed in points. After processing the answers to EPQ, we determined the level of neuroticism in each participant in the study. According to the results obtained, we divided the general group into three subgroups depending on the neuroticism level (low level of neuroticism - below 7 points, middle level of neuroticism - 8-13 points, high level of neuroticism- above 14 points).

In addition, EPQ allows researchers to estimate the sincerity

of answers. The results of testing by the above questionnaire allowed us to identify insincere answers and to exclude the respective data from the analysis of correlations between neuroticism (or physical aggression) and other parameters. Thus, the results of only twenty persons were taken into account during the correlation analysis between physical aggression or neuroticism and investigated hormones in total group, in the correlation analysis between all parameters in subgroups with middle neuroticism and high neuroticism.

Hormone levels in blood serum were measured using ELISA kits (Italy) for T3, T4 (thyroxine), Cortisol determination and a biochemical analyzer *Lab-Line-80* (Austria).

Statistics

Analysis of the obtained numerical data was performed using nonparametric approaches with Statistica 6.0 software; calculations of the Mann–Whitney *U* criterion, correlation analysis by Spearman and Multiple Linear Regression were applied.

Results

Persons with high and middle levels of neuroticism didn't differ in cortisol and thyroid hormones levels, but difference in thyroxine level was almost significant ($p=0.079$). In men with high neuroticism level it was higher than in individuals with middle neuroticism level (**Table 1**).

The levels of the abovementioned hormones correspond to reference range of ELISA kits: T3: 52-185ng/L, or 0.799-1.945 nmol/L; T4: 4.4-10.8 μ g/dL, or 56.637-139.018 nmol/L; Cortisol: 60-230ng/mL, or 166.459-638.091 nmol/L.

No correlation between thyroid hormones and physical aggression was found both in total group and in individuals with high and middle levels of neuroticism (**Table 2**).

In total group of participants, moderate positive correlations between neuroticism and T4, between T4 and cortisol were revealed (**Table 2**).

In men with high neuroticism level, the significant positive correlations between neuroticism and T₄, between T₄ and cortisol were observed (**Table 2**).

Table 1 Thyroid hormones and cortisol levels (nmol/L) in blood serum of men.

Hormones	Valid N	Median Me	Quartile 25%; 75%
Total group			
Triiodothyronine	32	2.015	1.915; 2.185
Thyroxine	32	128.700	114.545; 152.510
Cortisol	32	646.145	553.335; 770.875
Persons with high neuroticism level			
Triiodothyronine	10	2.150	2.050; 2.310
Thyroxine	10	146.720	115.830; 169.880
Cortisol	10	583.120	523.380; 830.870
Persons with middle neuroticism level			
Triiodothyronine	7	2.010	1.870; 2.140
Thyroxine	7	119.690	101.670; 135.900
Cortisol	7	582.620	388.610; 653.450

Table 2 Correlation coefficients between thyroid hormones and physical aggression, neuroticism and cortisol in men.

	Physical aggression	Neuroticism	Cortisol
Total group			
T4	-0.015	+0.49, p=0.029	+0.39, p=0.026
T3	+0.38	+0.44, p=0.0506	-0.13
Persons with high neuroticism level			
T4	+0.58	+0.78, p=0.008	+0.77, p=0.009
T3	+0.45	+0.013	+0.045
Persons with middle neuroticism level			
T4	-0.34	0.00	+0.36
T3	+0.37	0.22	-0.11

In men with middle neuroticism level, no correlation between investigated parameters was found (**Table 2**).

Correlation analysis between investigated parameters in persons with low neuroticism was not carried out due to the lack of such individuals.

Taking into account the above results and the data published by us earlier about interrelations between physical aggression (or neuroticism) and investigated hormones and correlations between hormones, we carried out multiple stepwise regression analysis involving not only T3 and T4 but also testosterone, estradiol, norepinephrine, epinephrine, and cortisol.

In persons with high level of neuroticism, multiple stepwise regression analysis revealed statistic significance of model (for physical aggression as dependent variable: Multiple R=0.99820310, F=92.50226, p=0.010733; for neuroticism as dependent variable: Multiple R=0.97481336; F=23.88123; p=0.001863). Significant predictors of physical aggression: norepinephrine - semi partial correlation=-0.62; p=0.004578; T3 - semi partial correlation=+0.58; p=0.005344; epinephrine - semi partial correlation=+0.478508; p=0.007750; T4 - semi partial correlation=+0.20; p=0.040924. The physical aggression is predicted by investigated variables on 99.64% (Regress. sums of squares: 1322.789; residual: 4.767; total: 1327.556). Estradiol is redundant variable.

Significant predictors of neuroticism: cortisol - semi partial correlation=+0.42; p=0.008278; T4 - semi partial correlation=+0.39; p=0.010753; epinephrine - semi partial correlation=+0.39; p=0.010860; estradiol - semi partial correlation=-0.38; p=0.012595. The neuroticism is predicted by investigated variables on 95.03% (Regress. sums of squares: 12.25837; residual: 0.64163; total: 12.90000). Testosterone, T3, norepinephrine are redundant variables.

In total group, physical aggression depends on testosterone (semi partial correlation=+0.45; p=0.044867), and neuroticism depends on T4 (semi partial correlation=+0.52; p=0.015761). The physical aggression is predicted by investigated variables on 31.43% (Regress. sums of squares: 2355.817; residual: 5139.867; total: 7495.684). The neuroticism is predicted by investigated variables on 49.60% (Regress. sums of squares: 143.7211; residual: 146.0289; total: 289.7500).

In persons with middle levels of neuroticism, the physical aggression depends on testosterone (semi partial correlation=+0.93; p=0.008638), and neuroticism depends on estradiol (semi

partial correlation=+0.96; p=0.020516). The physical aggression is predicted by investigated variables on 99.98% (Regress. sums of squares: 2482.932; residual: 0.402; total: 2483.333). The neuroticism is predicted by investigated variables on 96.06% (Regress. sums of squares: 14.27167; residual: 0.58547; total: 14.85714).

Discussion

Thyroid hormones are essential for normal growth and development of the fetus acting directly through anabolic effects on fetal metabolism and the stimulation of fetal oxygen consumption and indirectly by controlling the bioavailability and effectiveness of other hormones and growth factors that influence fetal development such as the catecholamines and insulin-like growth factors [7].

During fetal development and early neonatal period, they stimulate proliferation, differentiation, migration of neurons and glial cells, affect the processes of synaptogenesis and myelination of nerve fibers [8,9]. In the brain of adults, thyroid hormones affect the expression of a small number of neuron-specific genes, but the main effect of thyroid hormones in the central nervous system of adults is related to their influence on neurotransmitter neural transmission [10]. In particular, thyroid hormones affect the serotonergic, norepinephrinergic, dopaminergic neurotransmitter systems [11-15].

The influence of thyroid hormones on cardiovascular system is well established [16]. Thyroid hormone receptor signaling is required for the normal development of parvalbuminergic neurons (a population of newly discovered neurons in the anterior hypothalamus) directly linked to the regulation of cardiovascular function, including heart rate, blood pressure, and body temperature [17].

Thyroid hormone increase basal metabolic rate; they stimulate lipolysis/lipogenesis, β -oxidation of fatty acids, adaptive thermogenesis, gluconeogenesis, reduce insulin sensitivity, increase insulin metabolism etc. [17]. Metabolic status affects the emotional brain to maintain energy balance. Thyroid hormones are known fear controllers [18]. The central fear circuitry consists, among others, of subnuclei of the amygdala (the primary fear circuitry), the hippocampus, the medial prefrontal cortex (two major brain afferents), and the periaqueductal gray (a major output structure). The monoaminergic nuclei are most often reported to be involved in the elevation of fear. The amygdala

may be a major site of action of thyroid hormones, as in the basolateral amygdala, basomedial amygdalar nucleus, and lateral amygdala expresses the thyroid hormone receptors (Thra/b) to a relatively high level. In addition, the medial prefrontal cortex may be a major interaction site, as Tshr and Trhr are overrepresented in these brain regions [18].

The individual typological characteristics of the organism are based on the activity of four motivational emotogenic brain structures (frontal cortex, hippocampus, amygdala and hypothalamus). Lateral hypothalamus and medial hypothalamus are positive and negative emotogenic structures respectively [19]. Brain areas relevant for the control of aggression include cortex, amygdala, septum, hypothalamus, periaqueductal grey and the locus coeruleus [20]. The lateral hypothalamus and central amygdala are tightly involved in predatory aggression [21].

Monoaminergic brain systems have a great influence on the emotions and behavior in humans and animals and are involved in the development of both aggression and depression [22-23].

Thus, thyroid hormones can affect aggressiveness and neuroticism, at least in two ways: by their effects on neurotransmitter neural transmission and by the influence on metabolic status.

According to our results, persons with high and middle levels of neuroticism didn't differ in cortisol and thyroid hormones levels, but difference in thyroxine level was almost significant. In men with high neuroticism level it was higher than in individuals with middle neuroticism level. No correlation between thyroid hormones and physical aggression was found both in total group and in individuals with high and middle levels of neuroticism, but significant positive correlation between thyroid hormones and neuroticism was revealed in total group and in individuals with high middle levels of neuroticism.

We assume that thyroid hormones are indirectly involved in the aggression development through other hormones or mediators. This assumption is confirmed by the results of multiple stepwise regression and correlation analysis.

In persons with high level of neuroticism, physical aggression is predicted by norepinephrine, T3, epinephrine, T4, and neuroticism is predicted by cortisol, T4, epinephrine, estradiol.

The influence of the thyroid system on neurotransmitters (particularly serotonin and norepinephrine), which play a major role in the mood and behavior regulation, can contribute to the mood modulation mechanisms [24]. Some literature data strongly indicate a role for thyroxine in the process of formation of nerve fibres originating from the locus coeruleus neurons during perinatal development [25]. Thyroid hormones influence both neuronal development and anxiety via the thyroid hormone receptors [26]. It is shown that L-triiodothyronine enhances the action of antidepressant desipramine on the monoaminergic system in the prefrontal cortex in rats: it increases noradrenaline content in the prefrontal cortex, doesn't alter beta adrenoceptors in any brain region, decreases 5HT_{2A} receptors, significantly increases the dopamine turnover rate in the prefrontal cortex [27]. According to our early published data, significant negative correlation between noradrenaline level and physical aggression was observed in persons with high neuroticism level [28].

Hypothalamic pituitary adrenal (HPA) axis also plays an important role in the development of aggression. Human and animal studies have found associations between basal and acute levels of the stress-associated hormone cortisol and abnormal aggression [29]. Impulsive aggression is characterized by hypothalamic pituitary adrenal axis hyperactivity, and controlled aggression is characterized by low emotional activity [30,31]. There is evidence of the effect of both thyroid hormones on HPA axis and HPA axis on thyroid hormones. In women with borderline personality disorder, positive correlation between T₃ and cortisol is observed [4]. In our previous studies the significant positive correlation between neuroticism and cortisol level was found in persons with high neuroticism level [28].

The results of multiple stepwise regression analysis, the existence of significant positive correlations between neuroticism and T4, between T4 and cortisol together with the early published data about correlation between neuroticism and cortisol content in individuals with high neuroticism level indicate the involvement of thyroid hormones and cortisol in the formation of neuroticism in these persons. An indirect involvement of thyroid hormones in aggression development in persons with high neuroticism level is confirmed by the results of multiple stepwise regression analysis and by the significant positive correlation between neuroticism and physical aggression in this subgroup of participants [32].

The absence of correlations between the investigated parameters in persons with middle level of neuroticism supports our early suggestion that each of personality traits is a reflection of a complex interaction of many neurotransmitters (or hormones). The same hormone (or mediator) may be involved in the formation of different temperamental characteristics, and this overlapping can lead to unique combination of expression degree of personality traits [33]. According to the results of multiple stepwise regression analysis, in persons with middle levels of neuroticism, the physical aggression depends on testosterone, and neuroticism depends on estradiol. According to our previous findings, the strong positive correlations between blood serum estradiol content and neuroticism and between blood serum testosterone content and physical aggression are revealed in men with middle neuroticism level [28].

Obtained data indicate the necessity of participants division depending on expression degree of personality traits to study the mechanisms of aggression development. Thyroid hormones and cortisol are involved in the formation of high level of neuroticism, which is confirmed by the results of multiple stepwise regression analysis, by the existence of significant positive correlations between neuroticism and thyroid hormones, between thyroid hormones and cortisol together with our early published data about correlation between neuroticism and cortisol in individuals with high neuroticism level. In persons with high neuroticism level, thyroid hormones are indirectly involved in aggression development due to the results of multiple stepwise regression analysis, and significant positive correlation between neuroticism and physical aggression in these individuals.

The limitations of this study include a small sample size, but we plan to increase the sample size in the future, to conduct research not only on men but also on women of different ages and different populations. These studies will be important for understanding mechanisms of aggression development, because personality traits are the reflection of neurohumoral status.

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