Original Article

Effects of Thymoquinone on Hypothalamic *NPY* and *AgRP* Gene Expression in Intact and Hypothyroidism- Model Rats

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Abstract

Background & Objective: Thymoquinone is the most important compound of *Nigella sativa*, which stimulates the activity of thyroid axis in healthy individuals and people with hypothyroidism. The present study investigated the effects of thymoquinone on *Neuropeptide Y (NPY) and Agouti-dependent peptide (AgRP)* gene expression in the hypothalamus of healthy individuals and hypothyroidism- model rats.

Material & Methods: Twenty male Wistar rats weighing 190- 220g were used. Hypothyroidism was induced by a daily consumption of Methimazole (20mg/kg) for 42 days via drinking water. Control rats received the intraperitoneal injections of saline. Intact or hypothyroid rats received the intraperitoneal injections of thymoquinone (10mg/kg) for 15 days. One day after last injection, the thyroid gland and hypothalamic samples were dissected. Thyroid gland samples were used for histological study. Relative gene expression of hypothalamic *NPY* and *AgRP* was determined by real-time polymerase chain reaction.

Results: Thymoquinone significantly declined the *NPY* and *AgRP* gene expressions in the hypothalamus of intact rats in comparison with control group. Induction of hypothyroidism results in a remarkable increase in the *NPY* and *AgRP* gene expressions compared to control rats. In hypothyroid rats receiving thymoquinone, the mean relative *NPY* and *AgRP* gene expressions showed an insignificant decrease compared to hypothyroid group.

Conclusion: Because *AgRP/NPY* signaling pathway exerts inhibitory effects on thyroid gland function, thymoquinone may stimulate thyroid axis activity partly via inhibiting the hypothalamic *AgRP/NPY* gene expression in intact rats. In hypothyroidism, used dose of thymoquinone may not able to cause a significant decrease in *AgRP/NPY* gene expression due to its increased levels.

Keywords: Thymoquinone, Black Seed, Hypothyroidism, *AgRP, NPY,* Methimazole

Introduction

The thyroid gland is one of the most important endocrine glands in the body which is involved in regulating energy balance and basal body. Disorders of the thyroid gland include hypothyroidism and hyperthyroidism, and the latter is associated with clinical symptoms of anxiety, weight loss, increased appetite, heat intolerance, and reproductive disorders. On the other hand, hypothyroidism results from a decrease in thyroid hormone secretion, and its clinical symptoms include early fatigue, atony, lethargy, loss of appetite, hair loss, reproductive disorders, weight gain, mental and physical retardation in childhood (1, 2).

The activity of the hypothalamic pituitary thyroid (HPT) axis is regulated by various

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environmental factors or multiple excitatory or inhibitory intra-hypothalamic neurons upstream which is the site of thyrotropin-releasing hormone (TRH) synthesis in the hypothalamic paraventricular nucleus (PVN), the most important of which include neuropeptide Y (NPY) and Agouti-related peptide (AgRP) neurons. Their synthesizing neurons are located mainly in the hypothalamic arcuate nucleus (ARC) and synapse directly with TRH neurons or indirectly exert strong inhibitory effects on the HPT axis activity through intra-hypothalamic mediatory pathways (3, 4). Injection of NPY and AgRP to healthy humans and rats reduces energy expenditure and plasma levels of T3 and T4 hormones. Moreover, the syntheses of NPY and AgRP reportedly increase in patients with hypothyroidism, and they play an important role in weight gain by reducing energy intake, in addition to reducing the secretion of thyroid hormones (3-5). Thymoquinone is one of the most important compounds of black seed with the scientific name of Nigella sativa. Numerous pharmacological effects, including lowering blood sugar and fat, increasing insulin secretion, protecting liver and kidney tissues, and stimulating the secretion of sex and thyroid hormones, have been reported for black seed and its extracted thymoquinon (6-8). Previous studies have shown that the use of black seed and thymoquinone increases serum levels of T3 and T4 hormones and reduces serum TSH levels (7, 8). According to a recent report, thymoquinone causes the recovery of patients with hypothyroidism due to the its antioxidant effect. An increase in the secretion of T3 hormone after treatment with black seed was also reported in patients with hypothyroidism (7-9). Given the important role of NPY and AgRP neuropeptides in the regulation of the HPT axis, as well as the effects of thymoquinone on thyroid hormone secretion, the present study investigates the effects of intraperitoneal injection of thymoquinone on the mean relative gene expression of *NPY* and *AgRP* genes in the hypothalamus of healthy rats and those with methimazole-induced hypothyroidism.

Materials & Methods

Animals: In this experimental study, twenty adult male Wistar rats (8 weeks old and body weight: 190-220 g) were purchased from Iran University of Medical Sciences and were kept at 22 ± 2 °C in a 12 h light/ 12 h dark cycle, with free access to water and food during the project. All procedures for the maintenance and the use of experimental animals were approved by the research ethics committees of University of Mohaghegh Ardabili (code: IR.ARUMS.REC.1400.039).

Induction of hypothyroidism

To induce hypothyroidism, ten male rats received methimazole (20 mg/kg body weight, BW) in drinking water for 42 days (10). The induction of hypothyroidism was confirmed by hematoxylin –eosin staining of the sections of thyroid gland (Figure 1).

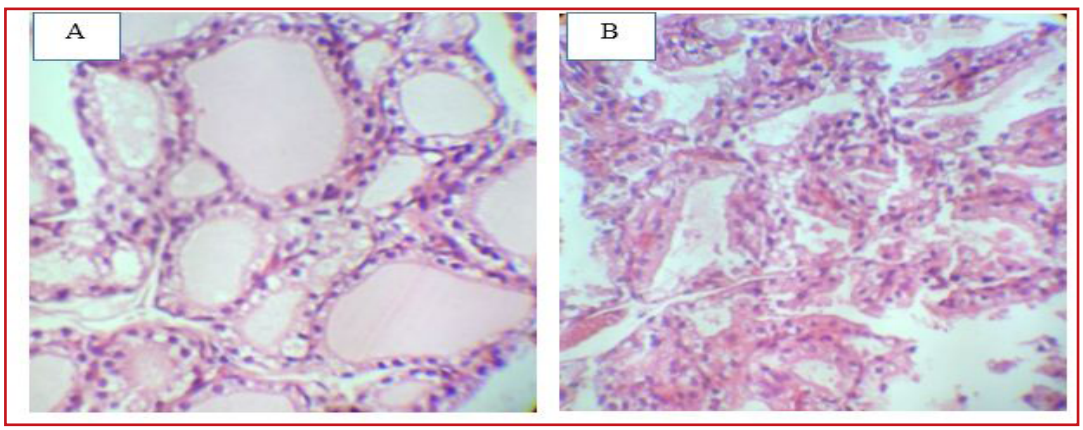

Figure 1. Representative images of thyroid gland stained by hematoxylin–eosin

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Figure A shows the architecture of normal follicles in control group in which follicles are lining with normal cubical cells and filled with colloid. Figure B shows the architecture of follicles in methimazole induced hypothyroidism model rats in which lumen of follicles is filled with the hypertrophy of lining cells and colloid material has been decreased in comparison with control group.

Injection of drugs and real-time polymerase chain reaction

In the first part of the study, ten intact rats were divided into two groups including A and B groups. Group A received intraperitoneal injection of saline as a control group. Group B received intraperitoneal injection of 10 mg/kg thymoquinone. In the second part of the study, ten hypothyroid rats were divided into two groups including C and D groups. Group C received intraperitoneal injection of saline. Group D received intraperitoneal injection of 10 mg/kg thymoquinone. In all groups, drugs were injected in a volume of 0.2 mL at 9 to 9:30 for 15 days.

To anesthetize rats, a ketamine and xylezine mixture (80 mg/kg BW + 100 mg/kg BW, respectively) was injected intra-peritoneally by an insulin syringe. After decapitation, the skull was cleaved by forceps to take out the brain. The hypothalamic sample was removed from the brain, and immediately immersed in liquid nitrogen for rapid freezing. Samples were then stored at −80 °C.

The total RNA of samples was extracted based on the acid guanidinium thiocyanate-phenol-chloroform method according to the instructions of the PureZol kit. The RNA concentration was determined using a NanoDrop device, and 1µg of RNA was then used for cDNA synthesis according to the instructions of a cDNA synthesis kit. The conditions of the PCR cycle are as follows: first denaturation 95 °C for 2 min, then by 40 cycles of denaturation at 95 °C for 5 sec, annealing at 54 °C for 25 sec (NPY), and annealing at 60 °C for 25 sec (AgRP, GAPDH) and extension at 60 °C for 20 sec. The sequences used for forward and reverse primers are shown in Table 1. The amplification products of NPY, AgRP, and GAPDH are 162 bp, 167 bp, and 120 bp, respectively. The expression of NPY and AgRP genes relative to the GAPDH in the RT-PCR reaction was determined using the formula $2^{-(\Delta\Delta Ct)}$.

Table1. Specific oligo nucleotide sequences for forward and reverse primers

	Primers Sequences
NPY: forward reverse	5'-TGGACTGACCCTCGCTCTAT-3' 5'- GTGTCTCAGGGCTGGATCTC-3'
AgRP: forward reverse	5'- AAGGCCATGCTGACTGCAA-3' 5'-CGGTCTGCTGCTGTCTTCTT-3'
GAPDH: forward reverse	5′- AAGAAGGTGGTGAAGCAGGCATC -3′ 5′-CGAAGGTGGAAGAGTGGGAGTTG-3′.

Statistical analysis

Data obtained were analyzed by SPSS software using one-way analysis of variance (ANOVA). Mean data were compared using Tukey's post hoc test. The results were presented as mean ± standard deviation of means (± SEM). In all statistical analyses, the results were reported at a significance of $P \leq 0.05$.

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Results

Mean relative gene expression of NPY in rats receiving thymoquinone (group B) decreased significantly compared with control group (group A) (P≤0.05, Chart 1). The mean relative gene expression of NPY in hypothyroid rats (group C) increased significantly compared with the control group (group A) (P≤0.05, Chart 1). The mean relative gene expression of NPY in the hypothyroid rats receiving thymoquinone (group D) decreased compared to the hypothyroid group, but this decrease was not statistically significant.

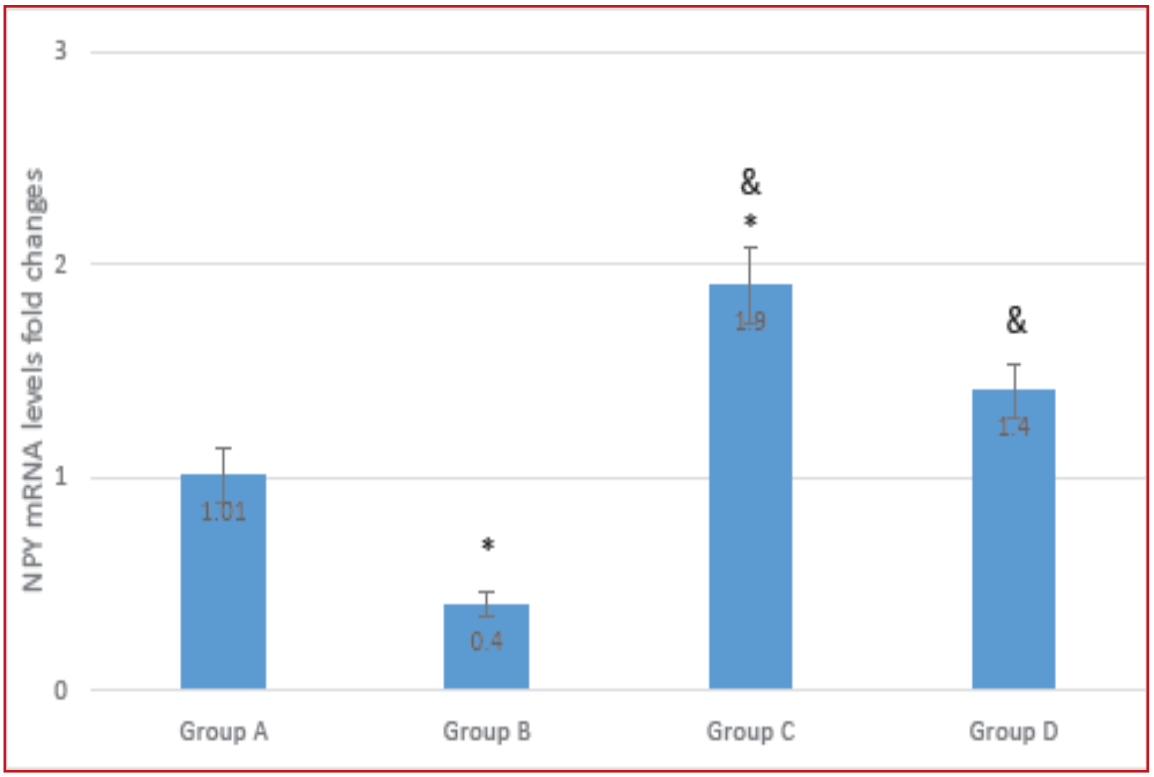

Chart 1. Mean relative gene expression of neuropeptide *Y (NPY)* in the hypothalamus of control rats (group A), intact rats receiving 10mg/kg thymoquinone (group B), hypothyroid rats (group C) and hypothyroid rats receiving 10mg/kg thymoquinone (group D). Results are presented as mean ± SEM and P≥0.05 is reported to be statistically significant. *: Compared to group A, &: Compared to group B

The mean relative gene expression of *AgRP* in the rats receiving thymoquinone (group B) significantly decreased compared to the control group (group A) (P≥0.05, Chart 2). The mean relative gene expression of *AgRP* in the hypothyroid rats (group C) increased compared to the control group (group A), which was statistically significant compared to the control group (group A) (P≥0.05, Chart 2). The mean relative gene expression of *AgRP* in the hypothyroid rats receiving thymoquinone (group D) decreased compared to the hypothyroid group (group C), but this decrease was not statistically significant (Chart 2).

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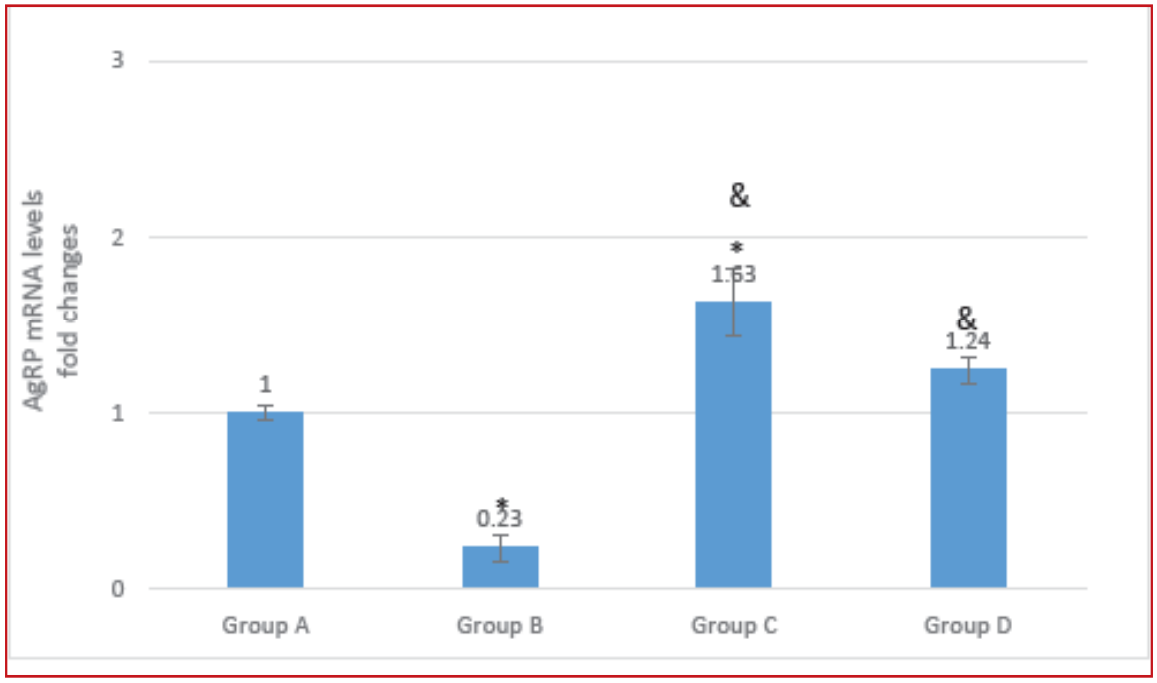

Chart 2. Mean relative gene expression of Agouti-dependent peptide *(AgRP)* in the hypothalamus of control rats (group A), intact rats receiving 10mg/kg thymoquinone (group B), hypothyroid rats (group C) and hypothyroid rats receiving 10mg/kg thymoquinone (group D). Results are presented as mean ± SEM and P≥0.05 is reported to be statistically significant.

*: Compared to group A, &: Compared to group B

Discussion

The analysis of data revealed that the induction of hypothyroidism resulted in a significant increase in the mean relative expression of *NPY/AgRP* genes compared to healthy saline-treated rats, which is in line with previous research. Similarly, an increase in the synthesis of *NPY/AgRP* was reported in people with hypothyroidism, which played an important role in the weight gain of these patients by reducing energy expenditure (3-5). Since AgRP is synthesized and secreted by the same NPY-secreting neurons, NPY leads to immediate feeding, whereas AgRP increases food intake on a delayed and prolonged timing scale (11). Nearly all NPY neurons are expressed with AgRP neurons in the hypothalamic ARC, i.e. there is a direct relationship between the expression of NPY and AgRP. Another study on the importance of NPY/AgRP in controlling the HPT axis activity reported that NPY/AgRP reduced energy expenditure and decreased plasma levels of T3 and T4 hormones (12, 13). It is also established that AgRP neurons in the ARC nucleus synapse with TRH neurons in the PVN nucleus, exerting a strong inhibitory effect on the HPT axis that inhibits TRH precursor mRNA in the PVN nucleus (12, 13).

The stimulatory effects of black seed or thymoquinone have been shown on the secretion of thyroid hormones in the previous studies (7-9). In the present study, the intrahypothalamic molecular mechanisms involved in the effects of thymoquinone on thyroid axis activity in male rats were investigated for the first time. The results revealed that thymoquinone significantly reduced the mean relative expression of NPY/AgRP genes in the hypothalamus of intact rats. Since NPY/AgRP neuropeptides are important inhibitory neuropeptides in the thyroid axis, the stimulatory effects of thymoquinone on the secretion of thyroid hormones may partly be through controlling the synthesis of these neuropeptides.

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This finding is consistent with studies showing that NPY/AgRP plays an effective role in energy homeostasis and the control of the HPT axis activity, in addition to regulating reproductive activity. In healthy humans and rats, it reduces energy expenditure and plasma levels of T3 and T4 hormones (12-14). Research has also shown that injection of thymoquinone increases plasma levels of T3 and T4 and, instead, it reduces serum levels of TSH (7).

According to the studies investigating the effects of thymoquinone on some hormones or peptides involved in the control of the thyroid axis activity, the following possible mechanisms can be summarized in the effects of thymoquinone on the mean relative expression of *NPY/AgRP* genes. Ghrelin is a 28-amino acid peptide which is mainly synthesized in the stomach, hypothalamic nuclei of ARC and PVN, and somewhat in other areas of the brain and peripheral organs and exerts its physiological effects through the growth hormone secretagogue receptor (GHSR-Ia) (15, 16). Injection of ghrelin increases the expression of *AgRP* and *NPY* genes in the hypothalamic ARC nucleus, and ghrelin exerts its stimulatory effects on the nutritional axis by increasing the synthesis of these neuropeptides (15, 16). It has also been found that the axons of NPY and AgRP neurons branch from the ARC nucleus directly on TRH neurons in the hypothalamic PVN nucleus (the main site of TRH neurons) and have receptors on TRH neurons. In addition, intracerebroventricular injections of AgRP and NPY both dramatically reduce thyroid hormone levels (3-5). The stimulatory effects of thymoquinone on the secretion of thyroid hormones have been reported in previous studies (7). Intraperitoneal injection of thymoquinone (10 mg/kg) for 15 days significantly reduced the mean relative expression of the ghrelin gene in hypothalamus of male rats Therefore, thymoquinone may be partially involved in stimulatory effects on the thyroid axis by reducing the synthesis of ghrelin, followed by a decrease in the synthesis of NPY and AgRP neuropeptides.

Oral administration of thymoquinone (10 mg/kg) in rats with propylthiouracil-induced hypothyroidism increased plasma levels of T3 and T4 hormones (7, 17). Intraperitoneal injection of black seed methanolic extract increased the levels of excitatory neurotransmitters, aspartate, glutamate, and decreased the levels of inhibitory neurotransmitters, gamma-aminobutyric acid (GABA) and glycine in the hypothalamus of male Wistar rats (18-20). Axons of GABAergic neurons have also been shown to branch off on TRH neurons of the hypothalamic PVN nucleus (18-20) and GABA inhibits the secretion of thyroid hormones. Ghrelin injection also increases GABA secretion by AgRP and NPY-synthesizing neurons and inhibits Pre Opiomelanocortin (POMC) neurons (18-20). Moreover, intraperitoneal injection of thymoquinone significantly reduced the mean relative gene expression of the ghrelin in the hypothalami of male rats (21).

Therefore, thymoquinone may be partially involved in inhibitory effects on the expression of *NPY* and *AgRP* genes and thus stimulating the thyroid axis activity by the direct inhibition of GABA release from hypothalamic neurons or indirectly by reducing the ghrelin synthesis, followed by reducing the release of intra-hypothalamic GABA.

Serotonin is a monoamine neurotransmitter, which is mainly secreted by serotonergic neurons of the central nervous system (CNS) and enterochromaffin cells in the gastrointestinal tract (21). The use of thymoquinone caused a significant increase in intracerebral serotonin levels and a significant decrease in levels of 5-hydroxy indole acetic acid (a metabolite derived from the breakdown of serotonin) (22). Another study revealed that intracerebral concentrations of norepinephrine and dopamine increase in rats with streptozotocin-induced diabetes, while serotonin intracerebral concentration decreased dramatically (23). Oral consumption of 10 mg/kg of thymoquinone decreased cerebral dopamine and norepinephrine levels and increased intracerebral serotonin levels in diabetic rats (23).

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Previous research also demonstrated that the injection of serotonin or serotonin agonists increased the secretion of thyroid hormones (24), and serotonin injection into the third ventricle of the brain decreased the secretion of ghrelin (25). Therefore, thymoquinone may partially exert an inhibitory effect on the expression of *NPY* and *AgRP* genes, thereby stimulating the thyroid axis activity, by the direct stimulation of serotonin release, or indirectly by serotonin-mediated reduction of the ghrelin synthesis.

As another mediator, dopamine is one of the most important neurotransmitters in the brain. The synthesis, release, and levels of NPY are regulated by dopamine (26, 27). In addition to the direct association of NPY neurons with TRH neurons, this neuropeptide can increase the activity of dopamine-secreting neurons in the tuberoinfundibular region (26, 27). Thus, high dopamine levels not only reduce TRH release from the median eminence, reduces TSH release from the anterior pituitary gland, and, ultimately, reduces the HPT axis activity. On the other hand, thymoquinone has an inhibitory effect on dopamine (28). Therefore, thymoquinone may play a role in the reduced expression of *NPY* by an inhibitory effect on dopamine.

Conclusion

The results demonstrate that thymoquinone may be involved in stimulating the thyroid axis activity by reducing the mean relative expression of *NPY/AgRP* genes. The present results also indicated that the methimazole-induced hypothyroidism in male rats significantly increased the mean relative expression of *NPY/AgRP* genes compared to saline-treated healthy male rats. However, the injection of thymoquinone into hypothyroid rats did not significantly reduce the mean relative expression of *NPY/AgRP* genes compared to control rats with hypothyroidism. The dose of thymoquinone used in hypothyroid rats might not have been sufficient to reduce their expression due to the elevated levels of these neuropeptides.

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Conflict of Interest

The authors have nothing to disclose. There is no conflict of interest in this article.

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