

Short Communication

Gastroprotective effects of *Nigella Sativa* oil on the formation of stress gastritis in hypothyroidal rats

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Abstract: The aim of this study was to assess the effects of hypothyroidism on the development of acute cold restraint stress gastritis in rats and protective effect of *Nigella sativa* at the beginning of the acute cold restraint stress. 60 rats were randomly divided into six groups; the control (groups I), surgically thyroidectomized group (group II), acute cold restraint stressed group (group III), surgically thyroidectomized plus stressed group (group IV), *Nigella sativa* oil group (group V) and surgically thyroidectomized plus stressed plus *Nigella sativa* oil group (group VI). Volume of gastric juice, number and size of ulcer, gastric malonaldehyde, gastric glutathione, gastric protein and serum thyroxine (T4) were measured. Significant increases both of number of gastric ulcer and malonaldehyde while decreases both of glutathione and protein levels in rats in groups III and IV in comparison with control group. While, insignificant increase were observed between control and both of groups II and VI. In rats, low thyroid hormone level increase stress gastritis, and this effect can be decreased by treatment with *Nigella sativa*.

Key Words: *Nigella Sativa* oil, stress gastric ulcers, hypothyroidal rats

Introduction

Thyroid hormones stimulate the biochemical processes involved in cell growth. Thyroxine increases the mitotic activity of cells especially in the crypts of digestive system in experimental animals such as rat [1]. Moreover, thyroxine has an important role in the gastric development [2]. Thyroid stimulating hormone and transformation of thyroxine to triiodothyronine (T3) are inhibited as a result of increased of glucocorticoid due to stress [3]. It has been reported that hypothyroid rats developed an increased numbers of ulcers [4]. However, experimental studies revealed a decreased incidence of ulcers in hyperthyroid rats [1]. Maralcan *et al.* [3] reported that the low level of thyroid hormone increases stress gastritis. This low thyroid hormone effects can be tolerated by thyroid hormone replacement therapy.

Gastric ulcer is a multifaceted disease with a complex pluricausal etiology that is not fully

understood. *Helicobacter pylori* is responsible for the majority of peptic ulcer. It weakens the protective mucus coating of the stomach and duodenum that allow acid to penetrate into the sensitive lining beneath [5].

Cold restraint stress causes gastric lesion by disturbance of the natural balance between the acid and its mucosal defense [6]. Therefore, increased acid secretion, reduced mucus, and bicarbonate secretion enhance contractility of the gastric wall and reduce it's mucosal blood flow [7]. In addition, increases of gastric free radicals and decreases of gastric antioxidant levels may be included among etiopathogenetic factors leading to stress based gastric ulcer. Therefore, antioxidant treatments are effective in prevention of stress induced ulcers [8].

The seed of *Nigella sativa* (NS) has been used traditionally for centuries in the Middle East, Northern Africa and Asia for the treatment of asthma [9, 10]. Recently, conducted clinical

and experimental researches have shown many therapeutic effect of NS such as immunomodulator [11], analgesic [12], anti-diabetic [13], anti-inflammatory [14], anticancer [15], bactericidal [16], diuretic [17], hypotensive [17, 18], antiallergic [19], anticestode and antinematode [20] and hepatoprotective [21]. Furthermore, the black seeds are important as a carminative and spice and used as a condiment in bread and others [22].

Experimental studies have demonstrated that the NS oil has gastroprotective activity against gastric mucosal injury [16] induced by ethanol [23, 24], ischemia reperfusion [25] and alcohol toxicity [21] in rats.

It is hypothesized that hypothyroidism is associated with exaggerated stress induced gastritis. Unfortunately no reports about NS in stress gastric ulcer in hypothyroidal rats are presented up to date. In this study a possible trail is made to delineate the protective role of NS oil against stress ulcer in rats. This was carried out in relation to its effect on different component of gastric secretion, gastric malonaldehyde and gastric glutathione levels.

Materials and methods

The present study was conducted on 60 adult male albino rats of Charles River strain (from Assiut university animal house). Males have been chosen in this study to avoid the hormonal changes, which may be faced in females. Rats have been selected for age (2-3 months) and weighted (150-200 grams). They were put at room temperature with the natural light dark cycle. The rats were fed a standard diet of commercial rat chow and tap water and left to acclimatize to environmental conditions for two weeks prior to inclusion in the experiment. All experiments were performed during the same time of day, between 9 a.m and 12 p.m to avoid variations due to diurnal rhythms [26]. Animals were randomly divided into six groups, each group containing 10 animals.

Group I: Control group

The rats in this group were allowed free access to food and water and were given physiological saline orally (10ml/kg. body weight) by gavage and were left without exposure to any form of stress [21, 24].

Group II: Surgically thyroidectomized group

After anesthesia, the rats were positioned to supine. After collar incision was done, thyroid was found in environment of trachea then, thyroidectomy was done with 22 gauge needle. Thyroid was dissected slowly, slightly and totally with needle. Then the wound was sutured with absorbable sutures [27]. To prevent the possibility of parathyroid disorder, 1% calcium gluconate was added to their water from date of operation.

Group III: Acute cold restraint stressed group

Rats were subjected to restraint by fixing the four limbs to a wooden board and placed in a refrigerator at 4 °C for three hours. According to Bhatnagar *et al.* [28] the door of the refrigerator was opened every ½ hour for inspection and follow up.

Group IV: Surgically thyroidectomized plus stressed group

The rats in this group were surgically thyroidectomized. Two weeks after the operation, these animals were subjected to acute cold restraint stress. The rats were then sacrificed.

Group V: Nigella sativa oil group

Rats in this group were treated orally with 10 ml/kg body weight NS oil from date of operation for 15 days [21, 24]. The rats were then sacrificed. NS oil was purchased from Kahira pharmaceutical & chemical industries co. (Cairo - Egypt).

Group VI: Surgically thyroidectomized plus stress plus Nigella sativa oil group

Rats in this group were surgically thyroidectomized and were treated orally with 10 ml/kg body weight NS oil from date of operation (for 15 days) [24]. Two weeks after the operation, these animals were subjected to acute cold restraint stress immediately after treatment and were then sacrificed.

At the end of the experiments rats were killed and the stomach was removed after oesophagus had been clamped. The gastric juice was collected and centrifuged and the volume was noted [5]. The stomachs were rapidly removed opened along the greater

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Table 1: The volume of gastric juice and ulcer index (UI) in stressed hypothyroidal rats (M±SE)

| Groups | Volume of gastric juice (ml) | UI (mm) |
|--|------------------------------|-------------|
| Group I: Control | 1.10±0.01 | 0.0±0.0 |
| Group II: Surgically thyroidectomized | 1.00±0.26 | 0.0±0.0 |
| Group III: Acute cold restraint stressed | 2.18±0.25* | 20.14±0.25# |
| Group IV: Surgically thyroidectomized plus stressed | 2.16±0.43* | 29.7±2.65# |
| Group V: <i>Nigella sativa</i> oil | 1.02±0.08 | 0.0±0.0 |
| Group VI: Surgically thyroidectomized + stress plus <i>Nigella sativa</i> oil) | 1.4±0.3 | 8.02±1.57 |

*Significant with control group; # Significant with group VI.

curvature and gently washed by 0.9 % NaCl solution. Scoring of ulcer was performed with the help of magnifying glass. Lesion size (mm) was determined by measuring each lesion and its greatest diameter recorded in the case of petechial lesions [21]. The grade of the lesions was scored as follows: no lesion = 0, 1-2 mm. = 1, 3-4 mm = 2, 5-6 mm = 4 and > 6 mm = 8. The mean ulcer index (UI) was calculated by dividing the sum of the total severity scores in each group by the number of animals in the same group [25]. The gastric mucosa was scraped with glass slides and frozen at -20 °C for subsequent biochemical determination.

Blood sampling

Blood samples were collected from hearts of rats immediately after killing and stored at -20 °C for further measurement of serum thyroxine (T4) which later measured by radioimmunoassay using the corresponding kits obtained from Immunochem Corp., Carson CA, USA.

Biochemical assays

Stomachs whole were cut into small pieces and homogenized (2 min. at 5000 rpm) in 4 volumes of ice cold tris-HCl buffer (50 mmol/L, pH 7.4). The 10% homogenate of gastric tissue was used for assay of malonaldehyde, glutathione and protein content.

The total amount of lipid peroxides in the serum was assayed by the thiobarbituric acid method described by Okhawa *et al* [29]. This measures the malonaldehyde equivalent substances, which are breakdown products of lipid peroxides. Glutathione was determined by spectrophotometric method based on the use

of Ellman's reagent [30]. Protein contents of all samples was determined according to the method of Lowry *et al* [31].

Statistical analysis

Statistical analysis was done using the computer software program prism (Comshare's version of a decision support system = DSS) version 3.3. The quantitative data were presented in the form of mean ± standard error (M±S.E). Student's t-test was done to compare between each two means. Also correlation coefficients were done. A probability less than 0.05 ($P<0.05$) was considered significant for all analyses.

Results

The data of the present work clearly demonstrated that the administration of NS oil were significantly decreased the volume of gastric juice and the number and size of gastric ulcer in group VI compared to groups III and IV. Number and size of gastric lesions were increased significantly in group IV rats as compared to that of group V animals while, insignificant increase were observed between group VI and each of groups I, II and V (**Table 1**).

Table 2 shows significant increase of gastric tissue malonaldehyde levels in rats in groups III and IV in comparison with control group. While, insignificant increase were observed between control and both of groups II, V and VI. There was a significant increase of gastric tissue malonaldehyde levels in groups III and IV as compared to that of groups II and V. The levels of gastric tissue glutathione were significantly decreased in groups II, III and IV

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Table 2: Effects of Nigella sativa oil on stressed hypothyroidal rats (M±SE)

| | Gastric malonaldehyde (nmol/g protein) | Gastric glutathione (umol/g protein) | Gastric protein (mg/g protein) | Serum T4 (nmol/L) |
|---|--|--------------------------------------|--------------------------------|------------------------|
| Group I: Control | 3.20±0.31 | 0.9±0.12 [#] | 41.1±1.91 | 60.2±10.7 [#] |
| Group II: Surgically thyroidectomized | 4.72±0.74 | 0.61±0.06 [#] | 30±1.2 ^{*#} | 5.1±0.2 [*] |
| Group III: Acute cold restraint stressed | 6.8±0.39 ^{*#} | 0.25±0.07 ^{*#} | 35±2.22 ^{*#} | 40±9.1 ^{*#} |
| Group IV: Surgically thyroidectomized plus stressed | 7.72±0.7 ^{*#} | 0.30±0.07 ^{*#} | 29.5±2.2 ^{*#} | 4±0.1 [*] |
| Group V: Nigella sativa oil | 2.99±0.12 | 1.5±0.70 | 42.2±2 | 65.8±8.2 |
| Group VI: Surgically thyroidectomized plus stress plus Nigella sativa oil | 3.9±0.7 | 1.3±0.12 [*] | 38.7±1.8 | 6.3±1.2 [*] |

*Significant with control group; [#]Significant with group VI.

rats as compared to that of groups I, V and VI. There were significant decreases of gastric tissue glutathione levels in groups III and IV as compared with group II (**Table 2**).

The obtained data revealed that NS oil administration significantly increased the gastric tissue protein as compared with groups II, III and IV rats. The levels of protein were significantly decreased in gastric mucosa groups II, III and IV rats as compared to that of groups I and V. While, insignificant changes were observed between control and both of groups V and VI (**Table 2**).

Table 2 shows significant decrease of serum T4 levels in rats in groups II, III, IV and VI in comparison with groups I and V. While, insignificant changes were observed between IV and both of groups II and VI.

Discussion

Experimental gastric ulcer may be assessed on the basis of number of gastric mucosal lesions. In the present study, a significant increase in the number of lesions in gastric mucosa was observed in groups III & IV animals. This is in accordance with an earlier report that showed that stress-induced lesion formation may be multifactorial, with stasis of gastric flow contributing significantly to the hemorrhagic as well as the necrotic aspects of

the tissue injury [5]. The prior gastric administration of NS resulted in significant reduction in the number of lesions in the gastric mucosa of group VI rats as compared to group IV rats indicating the protective effect of NS.

In the present study, the prior oral administration of NS resulted in significant reduction in the volume of gastric juice in group VI animals as compared to group IV rats. It probably did so by the neutralization of hydrochloric acid excessively secreted into the stomach. The neutralization of acid secretion in the stomach has already been reported to accelerate ulcer healing [32]. Significant increase in volume of gastric juice was noted in group in group III & IV rats as compared to groups I and II rats. Increased production of hydrochloric acid in the ulcerated condition might be a consequence of increased permeability of the mucosa, which is an important process in the development of ulcer [33]. Decreased of the volume of gastric juice in surgically thyroidectomized group may be due to low of thyroid hormones level. Fatemeh *et al.* [1] reported that decreased of thyroid hormone level has decreased the number of parietal cells in hypothyroid group. It is also probable that thyroid hormones exert their effects via affecting the parietal cells size or affecting the metabolic activity of these cells [32].

The level of protein was significantly decreased in the gastric mucosa of group II, III & IV rats as compared to that of group I rats. This indicated that acute stress caused the corrosion of gastric mucosa, resulting in the disruption of gastric mucosal cells. The net effect would be the loss of protein. Oral administration of NS significantly prevented the stress induced erosion of protein in the gastric mucosa of group VI rats [32].

Increased development of stress gastritis in hypothyroidism could be due to reduced metabolism, hypogastrinemia, or the reduced trophic effect of thyroxine on the gastrointestinal mucosa [33]. In cases of absent or insufficient thyroid hormone, the metabolic rate decreases and this decreased can cause a decreased in the rate of cell repair or renewal [3]. This result is in line with Money *et al.* [33], Kaynaroglu and Gokce [34] and Maralcan *et al.* [3].

The protective effect of NS oil against stress induced gastric ulcer may be explained by different mechanisms. It has reported that NS had an antihistaminic effect [35]. NS induced inhibition of histamine release to reduction in C-Amp level which may be due to inhibition of adenylase or stimulation of phosphodiesterase activity [36].

Recent studies showed that free radicals are one of the important factors in the pathogenesis of stress induced gastric mucosal damage. It was reported that stress causes severe oxidative stress in gastric tissue manifested as stimulated lipid peroxidation by increasing malonaldehyde content and decreasing of gastric glutathione content [8].

The anti-ulcerogenic effects of NS can be attributed to the improvement of the antioxidant status of animals due to an increase in mucin content of the gastric mucosa [37], or the presence of free radical scavenging substances such as thymoquinone [38]. NS inhibits free radical generation and increases serum levels of antioxidants [21, 39]. NS could protect the gastric mucosa by increasing the bioavailability of arachidonic acid, resulting in biosynthesis of the cytoprotective prostaglandins in the stomach [40]. Moreover, NS has also been reported to produce a marked inhibition on the release of leukotrienes, which cause mucosal tissue injury and hypoxemia [41]. T4 is decreased in

stressed groups due to the thyroid stimulating hormone and transformation of thyroxine to T3 is inhibited as a result of increased of glucocorticoid due to stress [3].

In conclusion, hypothyroidism increases stress gastritis, and this effect can be prevented by treatment with *Nigella sativa*.

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