International Journal of Basic and Applied Sciences. Vol. 6 No. 3. 2017. Pp. 104-111

Full length Research Paper

Histological and Ultrastructural Valuation of the Protective Role of Taurine Supplementation in Attenuating 5-Fluorouracil-Induced Thyrotoxicity in Adult Male Albino Rats

Hanaa R. Aboelwafa
Department of Biological and Geological Sciences, Faculty of Education, Ain Shams University, Roxy, Cairo, Egypt.

Article history
Received: 08-06-2017
Revised: 11-06-2017
Accepted: 18-06-2017

Corresponding Author:
Hanaa R. Aboelwafa
Department of Biological and Geological Sciences, Faculty of Education, Ain Shams University, Roxy, Cairo, Egypt.

Abstract
Thyroid dysfunction is a common endocrine toxicity of several anticancer drugs. 5-fluorouracil (5-FU) is a widely used antimetabolite for the treatment of various sorts of carcinomas. The current study aimed to investigate the influence of 5-FU on the histology and ultrastructure of thyroid glands of adult male albino rats and to evaluate the probable protective role of taurine (TAU) against 5-FU-triggered thyrotoxicity. Thyroid glands of twenty-four rats which were categorized into control, TAU, 5-FU and 5-FU+TAU groups were processed for light and transmission electron microscopic examinations. Manifestations of thyrotoxicity were evident in 5-FU-treated rats. Histologically, disorganized thyroid follicles represented as enlarged, collapsed and degenerated follicles were observed. Disrupted basal laminae, flattened or stratified lining epithelium, desquamated follicular cells, widening of the inter-follicular space with fibrosis and infiltrative inflammatory cells are also seen. Ultrastructurally, the majority of thyrocytes exhibited signs of apoptosis marked by hypertrophied cisternae of rough endoplasmic reticulum, cytoplasmic vacuolation and heterochromatic nuclei with irregular nuclear envelopes and dense chromatin masses. The apical borders of some follicular cells lost their microvilli. Administration of TAU to 5-FU-treated rats restored the normal histological and ultrastructural architectures of their thyroid glands. This study verified the protective influence of TAU against 5-FU-triggered thyrotoxicity in rats.

Key words: *5-Fluorouracil; Histology; Taurine; Thyroid Gland; Ultrastructure.*

Introduction

Chemotherapy is the most effective treatment pattern for cancers. Many cancer patients are suffered from developing thyroid dysfunction **[**1**]**. One of the most widely used chemotherapeutic agents is 5-Fluorouracil (5-FU) which is a fluorinated pyrimidine analogue utilized in the treatment of different sorts of solid tumors including breast, gastrointestinal, head and neck cancers both alone or in combination with other agents **[**2-4**]**. The cytotoxicity of 5-FU is fundamentally owing to the formation of its active metabolite, fluoro-deoxyuridine-monophosphate which inhibits the nucleotide synthetic enzyme, thymidylate synthetase and incorporates into cellular DNA and RNA as false pyrimidine base **[**5**]**.

Like other chemotherapeutic agents, 5-FU was reported to induce thyroid dysfunction which may possibly be due to alteration in thyroid hormones metabolism. This effect may be owing to the structural similarity between 5-FU and propylthiouracil which is a thioamide drug commonly indicated in the treatment of hyperthyroidism **[**6, 7].

Taurine (2-aminoethane sulfonic acid, TAU) is a sulphonic amino acid generally found in nearly all mammalian tissues, and it is derived from methionine and cysteine metabolism in the liver [8]. Endogenous biosynthesis of TAU is found to be insufficient, therefore it must be provided in the diet. TAU is found in particular foodstuffs like seafood, meats, eggs and milk [9]. TAU possesses different essential biological effects such as conjugation of bile acids, neuromodulation, immunomodulation, osmoregulation, anti-inflammation, detoxification, membrane stabilization and anti-oxidation [10- 12].

In the earlier studies, no information was available illustrating the influence of 5-FU in mammalian thyroid glands at the histological and ultrastructural levels. Therefore, the current study aimed to investigate the impact of 5-FU on the histological and ultrastructural architectures of the thyroid glands of adult male albino rats. In addition, the present study was conducted to evaluate the probable protective effect of TAU against such alterations that may be occurred in thyroid tissues of rats post 5-FU exposure.

Materials and methods

Pharmacological materials

5-FU was manufactured by Ebewe Pharma Ges.m.b.H. Nfg. KG. A-4866 Unterach, AUSTRIA. It is available as a clear colorless solution in a glass vial, each containing 250 mg of FU in a 5ml vial. TAU was purchased from Sigma Chemical Co. (St Louis, MO, USA) in a form of white crystalline powder.

Experimental animals

A total of twenty-four adult male albino rats (*Rattus norvegicus*) of similar ages (3-4 months) and weights (160-180 g) were used in the experiments after allowing one week acclimatization. The animals were obtained from the animal house of Theodor Bilharz Research Institute (TBRI), El-Giza, Egypt. They were allocated two per clear plastic cage with wood chips as bedding in a well-ventilated animal house at temperature of 25±2°C, relative humidity of 55±5% and a 12:12-h light–dark cycle. They were fed a standard diet and given water ad libitum. All animal experiments were done subordinate the protocols confirmed by the local Institutional Animal Ethics Committee of Ain Shams University.

Experimental protocol

The rats were randomly divided into four equal groups (6 rats each).

Group I (Control group): The animals were given 1 ml normal saline daily by oral gavage parallel to the treated groups throughout the course of the study.

Group II (TAU group): Taurine at a dose of 50 mg/kg bw. in distilled water (1 ml/animal) was applied to the rats orally once a day for 7 days using a gastric tube. This dosage was selected based on previous reports, in which 50 mg/kg of TAU showed enough in vivo pharmacological effects against the toxicity induced by various xenobiotics in rats [13, 14].

Group III (5-FU group): Rats were intraperitoneally (i.p.) injected with 5-FU (20 mg/kg bw/day) for 7 days. This dose was chosen depending on the work accomplished by El-Sayyad et al. [15] and Ali [16].

Group IV (Protective group): Rats were pretreated with TAU (50 mg/kg bw/day, orally) alone for 7 days and subsequently received 5-FU (20 mg/kg bw/day,i.p.) in association with TAU (50 mg/kg bw/day, orally) for other 7 days followed by treatment with TAU (50 mg/kg bw/day, orally) alone for other 7 days.

After the end of the specified experimental period, the rats were anesthetized using light ether and their thyroid glands were dissected out carefully and processed for the light and transmission electron microscopic (TEM) studies.

Histological preparations

Samples from the thyroid glands of control and experimental animals were rapidly fixed in aqueous Bouin`s fixative for 24 h. Then, they were subjected to the normal procedures for paraffin sectioning according to Bancroft and Gamble **[**17]. The haematoxylin-eosin (H&E) stained sections were examined with a light microscope and photomicrographs were made as required.

Ultrastructural preparations

Small pieces of the thyroid glands from both control and treated rats were immediately fixed in cold 4F1G (4% formalin+1% glutaraldehyde adjusted at pH 2.2) for 24 h, then they were post-fixed in 1% osmium tetroxide in 0.1M phosphate buffer (pH 7.3). After fixation, they were processed for ultrastructural evaluation by TEM as explained by Dykstra et al. [18]. The stained grids were examined and photographed by JEOL.JEM-1400-EX-ELECTRON MICROSCOPE at Electron Microscopy Department of TBRI, El-Giza, Egypt.

Results

Histological observations

Examination of the histological sections obtained from the thyroid glands of control and TAU-treated rats revealed normal histological architecture. The thyroid gland composed of follicles of different sizes. Each follicle appeared lined with a simple cuboidal epithelium of thyrocytes, filled with acidophilic homogeneous colloid and separated by capillary beds (Figs. 1A & 1B).

Whereas, examination of the thyroid gland sections of 5-FU-treated rats showed loss of their normal histological structure as illustrated in Figures (1C - 1E). Some follicles appeared enlarged and distended with colloid, others were completely collapsed, while the others were degenerated (Figs. 1C - 1E). Disruption of the basal laminae was seen in some follicles with their coalescence was also detected (Figs. 1C & 1D). Distorted thyroid follicles with flattening of their lining epithelium, detached and desquamated follicular cells in their lumens were observed in Figure (1E). Some follicles appeared with vacuolated colloid (Fig. 1E). Moreover, other follicles appeared lined with tall columnar or pseudostratified epithelium instead of the normal cuboidal epithelium (Fig. 1D). Some thyrocytes showed vacuolated cytoplasm and pyknotic nuclei as seen in Figures (1D &1E). Widening of the inter-follicular spaces with mesenchymal fibrosis and interstitial inflammatory cell infiltration were seen in-between the thyroid follicles (Figs. 1C & 1E). Examination of the thyroid gland sections of rats from the protective group revealed improvement in the histological changes detected post 5-FU treatment. The thyroid glands regain their normal architecture. However, some follicles appeared distended with colloid, thyrocytes appeared less vacuolated and the inter-follicular spaces appeared narrower than those of 5-FU-treated group (Fig. 1F).

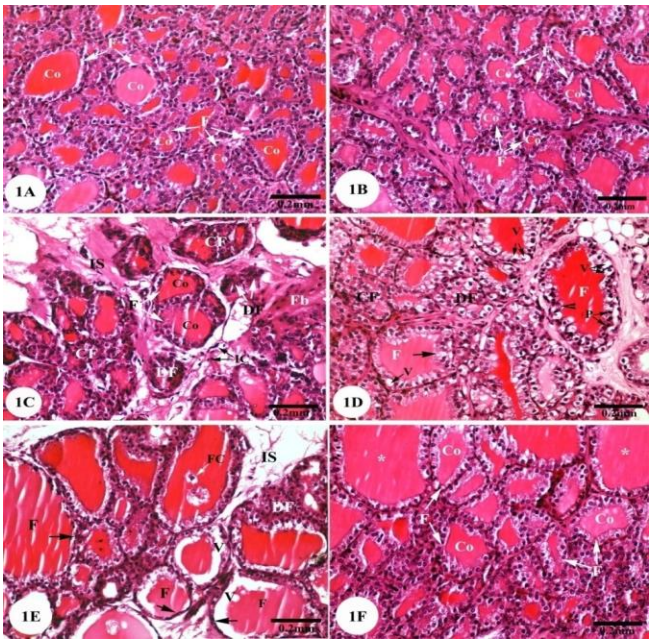

Fig. 1: Photomicrographs of the thyroid gland sections stained with H&E of control and treated rats showing **(A & B)** Normal architecture of thyroid follicles (F) being lined with cuboidal epithelium and filled with homogeneous acidophilic colloid (Co) in the control and TAU-treated rats, respectively. **(C)** Loss of the normal architecture of thyroid follicles (F) in 5-FU-treated rats where some follicles (F) are distended with colloid (Co), while the others appeared collapsed (CF) or degenerated (DF). Widening of the inter-follicular spaces (IS) with mesenchymal fibrosis (Fb) and interstitial inflammatory cell infiltration (IC) are also seen. **(D)** Enlarged thyroid follicles (F) appeared lined with columnar epithelium (arrow), whereas the others showing pseudostratified epithelium (arrowhead) are seen in 5-FU-treated rats. Cytoplasmic vacuolation (V) and pyknotic nuclei (P) of some thyrocytes, as well as collapsed (CF) and degenerated (DF) thyroid follicles are also observed. **(E)** Thyroid follicles (F) with flattening of their lining epithelium (arrows) and desquamated follicular cells (FC), besides vacuolation (V) of the follicular colloids are seen in 5-FU-treated rats. Degenerated follicles (DF), as well as increased inter-follicular spaces (IS) are also revealed. **(F)** Marked improvement of the thyroid follicle (F) structures with intact cuboidal lining epithelium and normal colloid materials (Co) are seen in the protective rats group. Some enlarged follicles (*) are also observed.

Ultrastructural observations

Transmission electron microscopic examination of the thyroid gland sections of control (Figs. 2A & 2B) and TAU-treated (Figs. 2C & 2D) rats showed that the thyroid follicles appeared lined with a single layer of cuboidal follicular cells surrounding a moderately electron-dense colloid. The thyrocytes appeared resting upon thin basal lamina and their apical borders had a moderate number of short microvilli that projected into the follicular lumen. Some thyrocytes were active and high in height having rounded euchromatic nuclei, while the others were more or less inactive and low in height possessing oval or irregular nuclei with dense clumps of heterochromatin. Their cytoplasm contained dilated cisternae of rough endoplasmic reticulum (RER), mitochondria, abundant apical vesicles containing colloid and scattered electron-dense granules.

On the other hand, the thyroid glands of 5-FU-treated rats revealed loss of the normal fine structural characteristics of their thyroid follicular cells as illustrated in Figures (3A - 3F). The majority of the thyroid follicular cells appeared with heterochromatic nuclei illustrating marked irregularity of their nuclear envelopes and dense chromatin masses (Figs. 3A & 3C). Stratification of the lining epithelium was seen in some thyroid follicles (Fig. 3A), while other follicles revealed squamous follicular cells with flat heterochromatic nuclei (Fig. 3B). The cytoplasm of the majority of these distorted follicular cells appeared with hypertrophied cisternae of RER with loss of their normal lamellar arrangement, electron-dense mitochondria, lysosomes and variable sized vacuoles (Figs. 3A - 3F). Many electron-lucent empty zones were seen in the cytoplasm which was devoid of organelles (Figs. 3E & 3F). Moreover, the nuclei of disrupted thyrocytes revealed different signs of deterioration post-5-FU administration. As seen in Figure (3D), invaginated nucleus with highly condensed peripherally heterochromatin and a wrinkled nuclear envelope were illustrated. Also, pyknotic nuclei surrounded by fragmented irregular nuclear envelopes and contained extensive electron-dense heterochromatin were observed (Fig. 3E). Furthermore, karyorrhectic nuclei with hardly distinct nuclear envelopes and fragmented heterochromatin, and euchromatin materials were noticed (Fig. 3F). The apical borders of some follicular cells exhibited disrupted microvilli (Figs. 3A, 3B & 3D), while the others showed loss of their microvilli (Fig. 3C). The thyroid follicular cells of rats from the protective group appeared more similar to the control group when examined by TEM. As illustrated in Figures (4A - 4C), the majority of thyrocytes

had nearly normal RER, mitochondria, secretory vesicles and euchromatic nuclei, as well as apical microvilli. However, few thyrocytes still have relatively dilated cisternae of RER, hyperchromatic nuclei and fragmented apical microvilli.

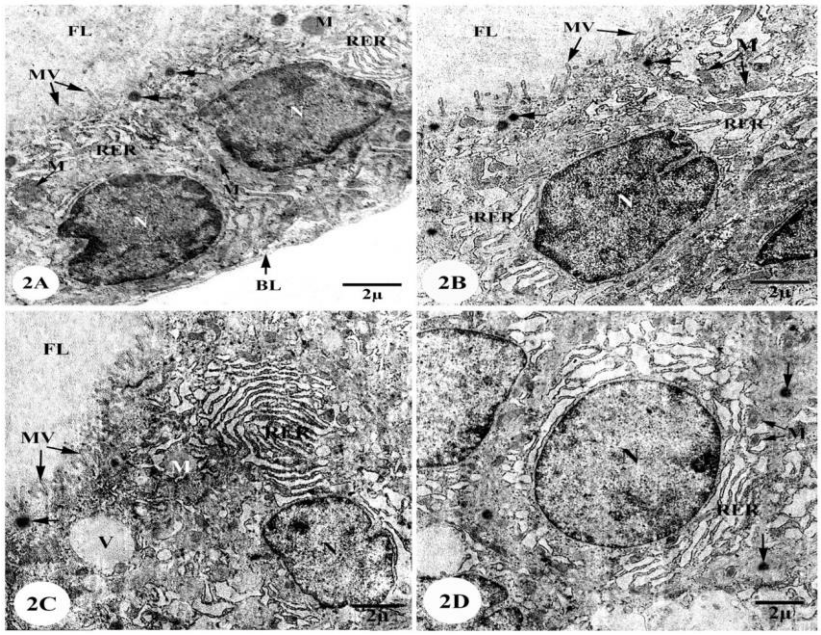

Fig. 2: Electron micrographs of the thyroid glands of control **(A & B)** and taurine-treated **(C & D)** rats showing normal cellular structure of follicular cells where their apical cytoplasm exhibit well-developed short microvilli (MV) projecting into the follicular lumen (FL) and the cells rest on thin basal lamina (BL). Each cell possesses dilated cisternae of RER, mitochondria (M), electron-dense vesicles (arrows), few vacuoles (V) and euchromatic nucleus (N).

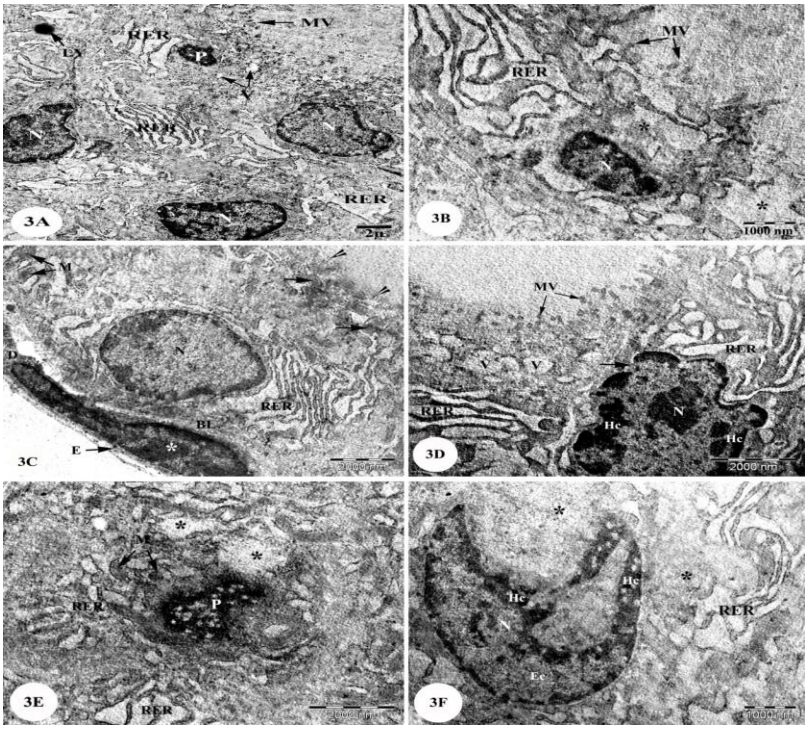

Fig. 3: Electron micrographs of the thyroid glands of 5-FU-treated rats showing **(A)** Stratification of the lining epithelium with the apical cells revealing disrupted microvilli (MV). Some thyrocytes show irregular heterochromatic nuclei (N) and the others exhibit pyknotic nuclei (P). Increased dilated cisternae of RER, lysosomes (Ly) and vacuoles (V) are seen in the cytoplasm. **(B)** Squamous thyrocyte possesses a flat heterochromatic nucleus (N), hypertrophied cisternae of RER, rarified cytoplasm (asterisks) and destructed microvilli (MV). **(C)** Distorted thyrocyte has heterochromatic nucleus (N), deformed mitochondria (M), markedly dilated cisternae of RER and apical electron-dense vesicles (arrows), as well as loss of the apical microvilli (arrowheads). Degenerated endothelial cell (E) of a blood capillary with an elongated heterochromatic nucleus (asterisk) and degenerated cytoplasm (D) is observed. **(D)** Deteriorated thyrocyte illustrating invaginated nucleus (N) with highly condensed heterochromatin (Hc) and a wrinkled nuclear envelope (arrow) is seen. Also, increased hypertrophied cisternae of RER, cytoplasmic vacuoles (V) and ruptured microvilli (MV) are observed. **(E)** Pyknotic nucleus (P) with highly condensed chromatin materials, broken cisternae of RER, electron-dense mitochondria (M) and vacuolated cytoplasm (asterisks) are displayed in deformed thyrocyte. **(F)** Degenerated thyrocyte showing karyorrhectic nucleus (N) with fragmented heterochromatin (Hc) and euchromatin (Ec). Hypertrophied stacks of RER and electron-lucent empty zones of cytoplasm (asterisks) are also noted.

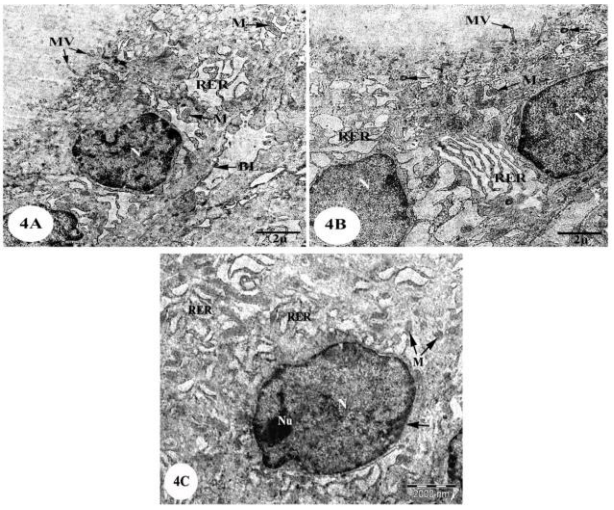

Fig. 4: Electron micrographs of the thyroid glands of the protective rats group showing **(A - C)** marked amelioration of the follicular cell ultrastructure where the cytoplasm appeared with nearly normal dilated cisternae of RER, mitochondria (M), electron-dense vesicles (arrows), euchromatic nuclei (N) and short apical microvilli (MV).

Discussion

The thyroid gland is a very important endocrine organ specialized for the production, storage and release of thyroid hormones thyroxine (T4) and triiodothyronine (T3) [19]. Thyroid hormones are involved in regulation of the metabolic rate of proteins, carbohydrates, lipids and energy expenditure in homeothermic animals [20]. Also, they are necessary for gastrointestinal motility, regulation of heart rate, reproductive functions, normal cell growth, and development, as well as for emotional stability [21]. On the other hand, disruption of thyroid function is correlated not only with general metabolic disturbance, but also with several distinctly unrelated health problems such as cardiac diseases, diabetes, lupus, reproductive difficulties and rheumatoid arthritis [22, 23].

5-FU is one of the most widely used antimetabolite which is indicated for the treatment of various sorts of carcinomas [2 - 5]. Unfortunately, utilization of 5-FU was reported to cause efficiency in thyroid hormones (T3 and T4) levels [6, 7]. Disorders of the thyroid gland are commonly correlated with cancer and chemotherapy [1]. Yet, the pathophysiology of thyroid toxicity triggered by various anticancer agents is not fully explained and for others, it remains speculative [24].Therefore, the current study was undertaken to investigate the influences of 5-FU in the histological and ultrastructural characteristics of the thyroid glands of rats. In addition, the present study aimed to evaluate the prospective ameliorating effect of TAU as a cytoprotective agent against 5-FU-induced thyrotoxicity.

The current histological results illustrated apparent distortion in the thyroid follicular structure of 5-FU-treated rats. Some follicles appeared distended with colloid and having flattened lining epithelial cells, others appeared collapsed and the majority appeared degenerated. Also, some deteriorated follicles appeared with stratified epithelium, disrupted basal laminae and desquamated follicular cells. The deformed thyrocytes showed vacuolated cytoplasm and darkly stained heterochromatic nuclei; some of them showing signs of pyknosis. Vacuolated colloid substances were also observed in the majority of altered follicles. Furthermore, widening of the inter-follicular space with fibrosis and interstitial lymphocytic infiltration in-between the thyroid follicles were noticed post-5-FU treatment.

In an attempt to explain these histological abnormalities, the distention of many thyroid follicles with their flattened follicular lining cells may appear as a result of increased colloid contents denoting hypoactivity of these follicles as previously reported by Abdel-Dayem and Elgendy [25] and El-Rouby [26]. They also reported that cellular distension with accumulated colloid resulted in cellular disruption and shedding of thyrocytes in the lumens. Furthermore, Nakazawa et al. [27] and El-Mehi and Amin [28] mentioned that these changes might disrupt the transport of colloid substance between the follicular lumen and the follicular cells causing the deficiency of thyroid hormone biosynthesis which indicating the hypofunctional condition of the thyroid gland. These results were in accordance with Li and Carayanniotis [25] who elucidated that the flattened follicular cells were metabolically inactive, whereas the cuboidal cells were active. They explained these results as iodide-mediated suppressive effects on the metabolic activity of some follicular cells. Also, Banu et al. [30] reported that follicular cell enlargement could be attributed to a sequence of cellular proceedings including genomic DNA damage, oxidative stress, and modulation of apoptotic regulatory gene p53.

The occurrence of tall columnar or pseudostratified epithelial lining cells of some deformed follicles coincided with the results of some authors who affirmed a significant increase in the height of the epithelium in hypothyroidism [31]. Also, the same authors recorded an elevation in TSH level which might be responsible for the proliferative activity of thyroid follicular cells. Most of the nuclei of follicular cells became heterochromatic with marked irregularity in their nuclear membranes. These results run parallel with those of other researchers who emphasized that the nuclear changes are indicative of cell apoptosis and necrosis [32].

Vacuolation of colloid and colloidal droplets in some follicular cells were attributed to the elevation of endocytotic activity to liberate the stored hormones, such vacuolation was under the impact of increased thyroid-stimulating hormone (TSH) [33]. Inter-follicular spaces were widened either as a result of the collapse of some follicles or due to necrosis of the others, leaving empty spaces [30]. Furthermore, collagen fibers were observed in the interstitial spaces between distorted follicles. Teng et al. [34] and Ruwhof and Drexhage [35] attributed the presence of these fibers to fibrosis of the thyroid gland that might occur in late stages of thyroid damage. In addition, they mentioned that the interstitial inflammatory cell infiltration occurred after apoptosis and necrosis of the follicular

cells due to the release of chemokines from these damaged cells in order to attract antigen-presenting cells, macrophages, T cells, and B cells into the thyroid gland. Then, these cells present thyroglobulin antigen to T cells and release various cytokines that induce T-cell activity.

The present ultrastructural results showed marked fine structural abnormalities in the thyroid follicular cells of 5-FU-treated rats. One of the most striking ultrastructural changes was the dilatation of cisternae of RER with the loss of their normal lamellar arrangement. Different explanations of such hypertrophy of RER were reported. According to Ghadially [36], dilation of RER may result from the synthesis of secretory products greater than their removal by transport mechanisms. This defect in the transport system of the RER, due to some enzymatic or mechanical abnormalities might prevent the removal of the normal quantities of synthesized materials. Also, they attributed this expansion of RER to the synthesis of abnormal secretory products that cannot remove by the transport mechanism. On the other hand, Jarrar [37] mentioned that dilatation of RER might reflect a need by the injured cells for oxidative enzymes which are required for detoxification. Coincides with the present results, RER expansion had been described in the thyroid follicular cells by Martino et al. [38] who emphasized that dilatation of RER was an evidence of disrupted protein synthesis which could be the result of retention of aberrant protein within the cisternae indicating a form of RER storage disease. This protein could not be processed, folded and transported to the convenient locations. Disruption in protein formation might prevent synthesis of apoptosis inhibitors and/or loss of fundamental proteins participated in cellular homeostasis causing cellular degeneration.

Vacuolization of the cytoplasm with the occurrence of many electron-lucent empty zones were detected in degenerated follicular cells post 5-FU exposure. Some researchers related the presence of such zones to markedly dilated RER stacks with rupture of some of them [26, 34, 35].

Also, the existing results manifested various apoptotic features of thyroid follicular cells of rats treated with 5-FU represented as increased irregularity of their nuclear envelopes, formation of condensed heterochromatin materials and multiple fragmentation of the nucleus, vacuolization of cytoplasm and swollen cisternae of RER as previously elucidated by Ihara et al. [39] and Sharma and Bhardwaj [40]. The disruption in protein production may prevent synthesis of apoptosis inhibitors such as Bcl-2 or loss of essential proteins involved in cellular homeostasis, leading to cellular death [38].

Some of the examined follicular cells lost their apical microvilli. This result was explained previously by El-Ghazawyet al. [41] who reported that the cells with no apical microvilli were metabolically inactive.

The exact mechanism of 5-FU-triggered thyrotoxicity is not fully explained. One probable mechanism is the production of free radicals that stimulate lipid peroxidation, lysosomal enzymes activation, cell membrane damage and apoptosis [42]. As reactive oxygen species (ROS) are found to be important mediators of anticancer drug-induced cytotoxicity [43, 44]. In addition, 5-FU caused thyroid dysfunction resulting in hypothyroidism in several patients [6, 7], and this hypothyroidism was reported to lead to excessive formation of ROS resulting in oxidative stress and subsequently lipid peroxidation and cell death [30]. Also, Jahani et al. [4] emphasized that 5-FU exerts its antitumor effect through inducing apoptosis. In the same context, Fujiwara et al. [6] clarified that thyroid disturbance caused by fluoropyrimidines including 5-FU may possibly result from alteration in thyroid hormone metabolism. This influence may be due to the structural similarity between 5-fluorouracil and propylthiouracil which is a thioamide drug widely utilized in the treatment of hyperthyroidism. It suppresses the thyroperoxidase activity that releases iodine for addition onto tyrosine residues on thyroglobulin for the production of T4 or T3, and also blocks the conversion of T4 to the active form T3 by inhibiting the enzyme 5'-deiodinase**.**

Data of the present investigation also illustrated that co-administration of TAU with 5-FU attenuated the thyrotoxicity-triggered by 5-FU, as the thyroid glands of rats in this group exhibited marked improvement in their histological and ultrastructural architectures. TAU, an efficacious non-enzymatic antioxidant, was reported to protect several organs in the body against toxicity and oxidative stress [8-12]. It may act directly to reduce oxidative stress by converting superoxides into taurochloramine that exhibits lesser oxidation [45], and indirectly via an assortment of mechanisms involving the renin-angiotensin system [46]. In the same context, Taş et al. [47] and Dirican et al. [48] verified that TAU supplementation protects against the increased oxidative stress that results from hypothyroidism by enhancing the activities of serum paraoxonase⁄arylesterase. In harmony with the present results, TAU was reported to ameliorate the thyroid function and thyroid gland histoarchitecture of the rats treated with chlorpyrifos and lead through its bioprotective and antioxidant properties [49].

Conclusion

The present study demonstrated that 5-FU induced hazardous histological and ultrastructural influences in the thyroid glands of adult male albino rats, and also illustrated that TAU improved the structure and fine structure of the thyroid glands of rats treated with 5-FU. Therefore, the current study proved that TAU has a protective effect against 5-FU-triggered thyrotoxicity. Such protective impact of TAU depends on the antioxidant and free radical scavenging effects. Supplementary studies at the levels of molecular biology are necessary to find out the exact mechanisms of the protective role of TAU.

Conflict of interest disclosure

The author announced that there are no conflicts of interest.

References

[1] J. Huang, L. Jin, G. Ji, L. Xing, C. Xu, X. Xiong, H. Li, K. Wu, G. Ren, L. Kong, Implication from thyroid function decreasing during chemotherapy in breast cancer patients: chemosensitization role of triiodothyronine. BMC Cancer 13 (2013) 334-345.
[2] N. Zhang, Y. Yin, S.J. Xu, W.S. Chen, 5-Fluorouracil: mechanisms of resistance and reversal strategies. Molecules 13 (2008) 1551–1569.
[3] K. Miura, M. Kinouchi, K. Ishida, W. Fujibuchi, T. Naitoh, H. Ogawa, T.I. Ando, N. Yazaki, K. Watanabe, S. Haneda, C. Shibata, 5-FU metabolism in cancer and orally-administrable 5-FU drugs. Cancers 2(3) (2010) 1717– 1730.
[4] M. Jahani, M. Azadbakht, F. Norooznezhad, K. Mansouri, L-arginine alters the effect of 5-fluorouracil on breast cancer cells in favor of apoptosis. Biomed Pharmacother 88 (2017) 114–123.
[5] T. David, H.C. Peter, T. Gregory, B. Catherine, S. Saurabh, In vivo effects of immunomodulators in a murine model of fluorouracil-induced mucositis. Curr Therap Res 72 (2011) 262–272.
[6] Y. Fujiwara, N. Chayahara, T. Mukohara, N. Kiyota, H. Tomioka, Y. Funakoshi, H. Minami, Hypothyroidism in patients with colorectal carcinoma treated with fluoropyrimidines. Oncol Rep 30 (2013) 1802-1806.
[7] M.A. Khan, D. Bhurani, N.B. Agarwal, Alteration of Thyroid Function in Indian HER 2-Negative Breast Cancer Patients Undergoing Chemotherapy. Asian Pac J Cancer Prev 16(17) (2015) 7701-7705.
[8] H. Ripps, W. Shen, Review: Taurine: A "very essential" amino acid. Mol Vis 18 (2012) 2673–2686.
[9] M.K. Ahmad, A.A. Khan, S.N. Ali, R. Mahmood, Chemoprotective effect of taurine on potassium bromate-induced DNA damage, DNA-protein cross-linking and oxidative stress in rat intestine. PLoS One 10(3) (2015) e0119137.
[10] J. Marcinkiewicz, E. Kontny, Taurine and inflammatory diseases. Amino Acids 46(1) (2014) 7-20.
[11] M.K. Ahmad, R. Mahmood, Protective effect of taurine against potassium bromate-induced hemoglobin oxidation, Oxidative stress, and impairment of antioxidant defense system in blood. Environ Toxicol 31(2016) 304–313.
[12] H.N. Yousef, H.R. Aboelwafa, The potential protective role of taurine against 5-fluorouracil-induced nephrotoxicity in adult male rats. Exp Toxicol Pathol 69 (2017) 265-274.
[13] M. Cetiner, G. Şener, A.Ö. Şehirli, E. Ekşioğlu-Demiralp, F. Ercan, S. Şirvanc, N. Gedik, S. Akpulat, T. Tecimer, B.C. Yeğen, Taurine protects against methotrexate-induced toxicity and inhibits leukocyte death. Toxicol Appl Pharmacol 209(1) (2005) 39-50.
[14] G. Sener, A.O. Sehirli, Y. Ipci, S. Cetinel, E. Cikler, N. Gedik, I. Alican, Taurine treatment protects against chronic nicotine-induced oxidative changes. Fund Clin Pharmacol 19(2) (2005) 155-164.
[15] H.I. El-Sayyad, M.F. Ismail, F.M. Shalaby, R.F. Abou-El-Magd, R.L. Gaur, A. Fernando, M.H.G. Raj, A. Ouhtit, Histopathological effects of cisplatin, doxorubicin and 5-flurouracil (5-FU) on the liver of male albino rats. Int J Biol Sci 5(5) (2009) 466-473.
[16] N. Ali, Protective effect of captopril against 5-fluorouracil-induced hepato and nephrotoxicity in male albino rats. J Am Sci 8(2) (2012) 680-685.
[17] J. Bancroft, M. Gamble, Theory and practice of histological techniques, 5th ed. London, Edinburgh, New York (2002).
[18] M.J. Dykstra, P.C. Mann, M.R. Elwell, S.V. Ching, Suggested standard operating procedures (SOPs) for the preparation of electron microscopy samples for toxicology/pathology studies in a GLP environment. Toxicol Pathol 30(6) (2002) 735-743.
[19] K. Boelaert, J.A. Franklyn, Thyroid hormone in health and disease. J Endocrinol 187 (2005) 1–15.
[20] B. Kim, Thyroid hormone as a determinant of energy expenditure and the basal metabolic rate. Thyroid 18(2) (2008) 141-144.
[21] G.E. Krassas, K. Poppe, D. Glinoer, Thyroid function and human reproductive health. Endocr Rev 31 (2010) 702–755.
[22] L.H. Duntas, J. Orgiazzi, G. Brabant, The interface between thyroid and diabetes mellitus. Clin Endocrinol 75 (2011) 1–9.
[23] K. Kumar, A.K. Kole, P.S. Karmakar, A. Ghosh, The spectrum of thyroid disorders in systemic lupus erythematosus. Rheumatol Int 32 (2012) 73–78.
[24] F. Torino, A. Barnabei, R. Paragliola, R. Baldelli, M. Appetecchia, S.M. Corsello, Thyroid dysfunction as an unintended side effect of anticancer drugs. Thyroid 23(11) (2013) 1345-1366.
[25] M.M. Abdel-Dayem, M.S. Elgendy, Effects of chronic estradiol treatment on the thyroid gland structure and function of ovariectomized rats. BMC Res Notes 2 (2009) 173-179.
[26] N.M. El-Rouby, A histological study on the effect of Diclofenac sodium (Declophen) administration on thyroid follicular cells of albino rats. Egypt J Histol 33(2) (2010) 213-223.
[27] T. Nakazawa, S. Murata, T. Kondo, N. Nakamura, T. Yamane, S. Iwasa, R. Katoh, Histopathology of the thyroid in amiodarone-induced hypothyroidism. Pathol Int 58 (2008) 55-58.
[28] A.E. El-Mehi, S.A. Amin, Effect of lead acetate on the thyroid gland of adult male albino rats and the possible protective role of zinc supplementation: A biochemical, histological and morphometric study. J Am Sci 8(7) (2012) 61-71.
[29] H.S. Li, G. Carayanniotis, Induction of goitrous hypothyroidism by dietary iodide in SJL mice. Endocrinology 148 (2007) 2747–2752.

[30] S.K. Banu, J.A. Stanley, J. Lee, S.D. Stephen, J.A. Arosh, P.B. Hoyer, R.C. Burghardt, Hexavalent chromium-induced apoptosis of granulosa cells involves selective sub cellular translocation of Bcl-2 members, ERK1/2 and p53. Toxicol Appl Pharmacol 251(3) (2011) 253–266.
[31] R. Dallaire, E. Dewailly, D. Pereg, S. Dery, P. Ayotte, Thyroid function and plasma concentrations of polyhalogenated compounds in lnuit adults. Environ Health Persp 117(9) (2009) 1380-1386.
[32] L. Zhang, S., Sharma, L.X. Zhu, T. Kogai, J.M. Hershman, G.A., Brent, S.M. Dubinett, M. Huang, Nonradioactive iodide effectively induces apoptosis in genetically modified lung cancer cells. Cancer Res 63 (2003) 5065–5072.
[33] H. Wang, Z. Yang, B. Zhou, H. Gao, X. Yan, J. Wang, Fluoride-induced thyroid dysfunction in rats: roles of dietary protein and calcium level. Toxicol Ind Health 25 (2009) 49–57.
[34] X. Teng, Z. Shan, W. Teng, C. Fan, H. Wang, R. Guo, Experimental study on the effects of chronic iodine excess on thyroid function, structure, and autoimmunity in autoimmune-prone NOD.H-2h4 mice. Clin Exp Med 9 (2009) 51–59.
[35] C. Ruwhof, H.A. Drexhage, Iodine and thyroid autoimmune disease in animal models. Thyroid 11 (2011) 427–436.
[36] F.N. Ghadially, Endoplasmic reticulum. In: Ultrastructural pathology of the cell and matrix (Ghadially, F.N. eds), Boston, Butter-Worth-Heinemann, (1997) 433–602.
[37] B.M. Jarrar, Ultrastructural alterations in proximal tubule cells induced by lead. Pakistan J Biol Sci 4(10) (2001) 1281-1284.
[38] E. Martino, L. Bartalena, F. Bogazzi, L.E. Braverman, The effects of amiodarone on the thyroid. Endocr Rev 22 (2001) 240–254.
[39] T. Ihara, T. Yamamoto, M. Sugamata, H. Okumura, Y. Ueno, The process of ultrastructural changes from nuclei to apoptotic body. Virchows Arch 433 (1998) 443–447.
[40] R.K. Sharma, J.K., Bhardwaj, Ultrastructural characterization of apoptotic granulosa cells in caprine ovary. J Microsc 236 (Pt 3) (2009) 236–242.
[41] I.F. El-Ghazawy, I.P. Kelada, S.H. Safwat, T.M. Zeitoun, S.K. Sawires, Histology study of the effect of amiodarone on the follicular cells of the thyroid gland of male albino rats. Bull Alex Fac Med 43 (2007) 747–753.
[42] C.J. Xian, G. Howarth, J. Cool, B. Foster, Effects of acute 5-fluorouracil chemotherapy and insulin-like growth factor-I pretreatment on growth plate cartilage and metaphyseal bone in rats. Bone 35(3) (2004) 739-749.
[43] F. Oktem, F. Ozguner, O. Sulak, S. Olgar, O. Akturk, H.R. Yilmaz, I. Altuntas, Lithium-induced renal toxicity in rats: protection by a novel antioxidant caffeic acid phenethyl ester. Mol Cell Biochem 277(1-2) (2005) 109-115.
[44] H. Parlakpinar, S.Tasdemir, A. Polat, A. Bay-Karabulut, N. Vardi, M. Ucar, A. Acet, Protective role of caffeic acid phenethyl ester (cape) on gentamicin-induced acute renal toxicity in rats. Toxicology 207(2) (2005) 169-177.
[45] C. Kim, Y.N. Cha, Production of reactive oxygen and nitrogen species in phagocytes is regulated by taurine chloramine. Adv Exp Med Biol 643(2009) 463–472.
[46] J. Hu, X. Xu, J. Yang, G. Wu, C. Sun, Q. Lv, Antihypertensive effect of taurine in rat. Adv Exp Med Biol 643 (2009) 75–84.
[47] S. Taş, M. Dirican, E. Sarandöl, Z. Serdar, The effect of taurine supplementation on oxidative stress in experimental hypothyroidism. Cell Biochem Funct 24 (2006) 153–158.
[48] M. Dirican, S. Taş, E. Sarandöl, High-dose taurine supplementation increases serum paraoxonase and arylesterase activities in experimental hypothyroidism. Clin Exp Pharmacol Physiol 34 (2007) 833–837.
[49] M.G. Akande, M. Shittu, C. Uchendu, L.S. Yaqub, Taurine ameliorated thyroid function in rats co-administered with chlorpyrifos and lead. Vet Res Commun 40(3-4) (2016) 123-129.