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STUDY ON PATHOLOGICAL CHANGES ASSOCIATED WITH EXPERMENTAL THYROTOXICOSIS IN RATS

Sattar R. Suhail AL-Akaby & Khalil H. Zenad AL-Jaboori

Department of Pathology & Poultry Diseases, College of Veterinary Medicine, University of Baghdad, Iraq

ABSTRACT

The study was designed to evaluate the histopathological parameter associated with experimental thyrotoxicosis due to thyroxine (T4) injection in rats. Three groups of rats (5/ group) were injected with (2.5, 7.5 and $10 \mu g$ /100 gm body weight subcutaneously) of T4, the control group was injected 2.5ml/100 gm of physiological saline for 60 days, at the 40th and 50th day the animals were injected subcutaneously with *Candida albicans* antigen. At 60th day of injection the animals were sacrificed and all organs were taken. Results showed different pathological lesions in different organs, such as complete inhibition in thyroid tissue, increase in the colloid and flattening of epithelial lining of the thyroid gland, hypertrophy of heart due to acute cellular swelling, hypertrophy in the kidney resulted from cloudy swelling, hydropic degeneration. Liver showed centrilobular necrosis following the cloudy swelling and hydropic degeneration in the area adjacent to the central veins, Pancreas there was atrophy of islets of langerhans resulted from reduction of - cells region. There was extensive reactive hyperplasia in both T-cell and B-cell regions of white pulp of the spleen and in the cortical region of lymph node. There was elongation (hyperplasia) in the zona fasiculata and reticularis of the adrenal cortex on the expense of medulla. Brain tissue showed extensive perinuerounal edema and focal gliosis. Hyperplasia of peyer patches and goblet cells with mucous production in the intestinal lumen. Lung showed interstitial thickening due to infiltration of inflammatory cells, hyperplasia of pneumocyte type and congestion of alveolar capillaries testis were atrophied, loss of spermatogenesis and hydropic degeneration of the germinal epithelia lining of somniferous tubules and atrophy of levdig cells. Ovaries were atrophied and reduced in the number of growing follicles and increase in the luteal tissue formation. Uterus showed thickening of subendometrial fibrous tissue layer with too much collagen production, reduction in the number of endometrial glands and metaplasia of endometrial epithelia. Skin showed extensive sclerosis due to much collagen production and extensive edema seen in different organs.

KEYWORDS: Thyrotoxicosis, Pathological changes, Thyroxin, Rats etc.

INTRODUCTION

Thyroid hormones (T4, T3) secreted from thyroid gland, thyroid gland and thyroid hormones regulate growth, development and cellular metabolism^[1]. Thyroid hormone plays a role in cardiovascular, nervous, immune, and reproductive system development and function^{[2].} Thyroid hormones modulate the immune response therefore they play a role in cellular and humoral immunity^[3]. Thyroid disorder is a general term representing several different diseases due to disturbance in thyroid hormones and thyroid gland and there are two major categories of thyroid disorders. hyperthyroidism hypothyroidism, and depending on thyroid hormone levels as increased or decreased respectively, the most common type of hyperthyroidism is produced by a generalized over activity of the entire thyroid gland^[4]. Hyperthyroidism (excess of thyroid hormone) causes symptoms include tachycardia, dyspnea, Atrial fibrillation, ployphagia, polyuria, polydipsia, and nervous signs ^[5, 6]. In hyperthyroidism, there is increase in gluconeogenesis in the liver and glucose efflux through hepatocyte plasma membranes and it cause decrease in body weight, as well as decrease in plasma lipids such as plasma cholesterol and triglycerides ^[7, 8]. Also hyperthyroidism associated with hypertrophy of heart and kidney, and degenerative changes in liver $^{[9, 10]}$.

MATERIALS & METHODS

One to one and half months old rats (average body weight 100gm) were randomly divided into four groups, each group consists of 10 rats (5 rats of each sex per group) and were treated daily for 60 days as follow:- Group1; rats of this group were received 2.5 μ g /100gm of body weight of thyroxine injected subcutaneously (s/c); Group 2; rats of this group were received 7.5 μ g /100gm of body weight of thyroxine injected subcutaneously (s/c); Group 3; the rats in this group were received 10 μ g /100gm of body weight of thyroxine injected subcutaneously (s/c); and animals in group 4 were received 2.5ml /100gm of body weight of saline injected subcutaneously (s/c) and considers as control group.

At 40 days of experiment immunized animals by inoculation 0.25 ml s/c of whole killed antigen of *Candida albicans* (9X10⁸ CFU / ml) and the booster dose was inoculated 0.5 s/c at 50 days of experiment. At the end of experiment, the animals were sacrificed and postmortem were done for all animals, the macroscopic appearances were recorded to detect any abnormal gross changes in internal organs, specimens were taken from all internal organs; the tissues were kept in 10% formaldehyde immediately after removal. After 48 hours of the fixation, then processing was routinely done with a set of increasing alcohol concentrations, tissues section

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were embedded in paraffin blocks, and sectioned by microtome at 5μ m for all tissues. All tissues were stained with hematoxylin and eosin stain and the histopathological changes were observed under light microscope^[11].

RESULTS & DISCUSSION

Different pathological findings were present in different groups of the animals but more extensively observed in group :



FIGURE1: Thyroid gland: increase the colloid of thyroid follicles (← →) and flattening of epithelial lining (→) (400X H&E).

Liver

The result showed mild degenerative changes in the liver including mild cloudy swelling and hydropic degeneration , these degenerative changes occur in the areas adjacent to the central vein which developed into coagulative type of necrosis and perivascular leukocytes cuffing were seen in certain sections (Figure 2), this results agree with ^[14] and explain on the basis of the mechanism of this injury appears to be relative hypoxia in the perivenular regions, under high T4 effect and due to an increase in hepatic oxygen demand without an appropriate increase in hepatic blood flow.



FIGURE 3: Pancreas atrophy of islets of langerhans () especially - cell region (200 X H&E).

Thyroid glands

Showed complete regression of their size (atrophied) and increase the colloid and flattening of epithelial lining in this study we result from extensive hyperthyroidism state (T4) which was evident in different groups of animals especially group (Figure 1), this hyperthyroidism state cause complete thyroid atrophy and enhance Hypothalamic–pituitary–adrenal axis (HPA axis), similar findings reported by^[12, 13] that thyroid tissue alteration and reduced functions due to hyperthyroidism were resulted into HPA axis functions and increases ACTH and corticosteroid productions.



FIGURE 2: Liver Extensive hydropic degeneration (↔) with vacuolation of hepatocytescytoplasm (→) and congestion of blood vessels (→) (200 X H&E).

Pancreas

In this study, the main lesions in this organ were atrophy of islets of langerhans region especially - cell region of pancreas (Figure 3), this result reported by the long term of thyrotoxicosis has been showed to cause beta cells (cells) dysfunction resulting in reduced pancreatic insulin content, poor insulin response to glucose and decreased rate of insulin secretion ^[15]. In the other studies in rats, exogenous T4 treatment has been shown to acutely increase the rate of -cell apoptosis and increase glucose transporter 2 (GLUT-2) levels in hepatocyte plasma membranes resulting in the increase in glucose efflux across the hepatocyte plasma membrane in the final step of hepatic glucose production ^[16,17,18].



FIGURE 4: Kidney: cloudy swelling in proximal convoluted tubule showed star–shape lumen (\longrightarrow) and swelling of their epithelia, also dilation of Bowm ans space (\longrightarrow) (200 X H & E).

Kidneys

In this study there is hypertrophy of kidneys grossly and microscopically ,there are mild cloudy swelling and hydropic degeneration were seen in proximal and distal convoluted tubules with dilation of Bowman's space, also there is infiltration of lymphocytes between renal tubules (Figure 4) ,this result observed by^[19,20] and explained as a result of thyroid hormone (T4) activates the circulating or intrarenal renin–angiotensin system (RAS) via enhancement of renal renin mRNA expression, which then leads to renal hypertrophy induced by thyroxine (T4) administration in rats in this study .

Adrenal glands

The main lesions in this organ were elongation of zona fasiculata and zona reticularis layers, on the expanse of medullary regions (Figure 5), these cortical hyperplastic lesion were occurred under effect of disorder of thyroid tissue due to hyperthyroidism (T4) which was evident in all groups of thyrotoxicosis, especially group of this experiment .A similar findings in rats recorded by^[13] on that the altered thyroid function *i.e.* hyperthyroidism affect the secretion and metabolism of adrenocortical hormones which resulted from adrenocortical hyperactivity which was evident in this study .



FIGURE 5: Adrenal gland: there is elongation of zona fasiculata () and reticularis (of their cells and reduced in the size of medulla ((200 X H&E).



FIGURE 7: Lung: interstitial thickening and there is thickening of alveolar wall due to proliferation of pneumocyte type () and some inflammatory cells infiltration (lymphocyte and macrophage) and preibronchial lymphoid tissue hyperplasia () which mphysematous area () (2000) H&E).

Similarly ^[12, 13] reported that the duration and severity of hyperthyroidism state is important factors for increased functional capacity of adrenal cortex and the Hypothalamic–pituitary–adrenal axis (HPA axis) function which resulted in the secretion of glucocorticoide and mineralocorticiods that increase the level of sugar in the body and increase retention of sodium Na+ and H2O which resulted in edema in different groups of rats respectively which was evident in this study.

Brain

Showed extensive demyelination and perineruonal edema in adjacent glia cells and purkinje cells which were present in all examined sections in different groups of animals and in certain cases there was perivascular leukocyte cuffing and focal gliosis due to proliferation of microglia cells (Figure 6). Because thyroid hormones play a role in regulation of nervous system myelination of growth and puberty and proliferation of cells such as glia cells also regulates oligodendrocyte production of myelin ^[21, 22], the possibility that prolonged hyperthyroidism could activate apoptotic mechanisms in the myelin forming cells , these results indicate that one of the actions of sustained levels of thyroid hormones in the rat is to increase oligodendroglia cell death by apoptosis this findings also observed by ^[23].



FIGURE 6: Brain: focal gliosis (characterized by focal proliferation of microglia cells and perineuronal edema () around glia cell (X200 H&E).



FIGURE 8: Intestine: extensive mucin production in the lumen () and hyperplasia of goblet cells () (200 X H&E).



There is thickening of alveolar wall due to congestion of alveolar capillaries and proliferation of type pneumocytes and peribronchial lymphoid tissue hyperplasia, in certain section extensive emphysematous areas were seen in the pulmonary tissue in addition to pulmonary edema (Figure 7), these changes occur as a result of thyrotoxicosis which lead to increase O2 consumption due to increased basal metabolism due to elevated thyroid hormones consequently, the radical oxygen species production increases in lungs this might result in cellular damage in the lung^[24]. In other study by ^[25] explained the basis of the thyrotoxicosis effect on the aleveolocapillary permeability via affect on surfactant that



FIGURE 9: Peyer patches of intestine: There is extensive proliferation of lymphoid tissue () with germinal center formation (100 X H&E).



FIGURE : Lymph node: reactive hyperplasia of lymphoid follicle in cortical region (\checkmark) with secondary lymphoid follicle formation (200X H&E).

Spleen and Lymph nodes

The main lesion in spleen were hyperplasia of white pulp in which proliferation of the lymphocyte and macrophages in the periarterial sheath region (T-cells) and in remainder area of white pulp (B-cell region) (Figure 10), also reticulo-endothelial cells hyperplasia observed in red pulp. Whereas in lymph nodes reactive hyperplasia of lymphoid follicles in the cortical regions (Figure 11), with secondary lymphoid follicles due to lymphocytes and macrophage proliferation these findings were recorded by ^[27] as result of good immune response of body under effect of thyrotoxicosis due to high T4 level which was evident in this experiment . postulated that surfactant amount increase in thyrotoxicosis due to proliferation of type pneumocytes, for peribronchial lymphoid tissue hyperplasia occur as a result of the immunological effect of T4 on these tissues. **Intestine**

Showed mucinous degeneration in which secretion of mucin in the lumen of intestine and hyperplasia of goblet cells in addition to hyperplasia of payer patches (Figure 8,9), this finding were observed by ^[26] that the hyperplasia of goblet cell and payers patches resulted from the good immune response of the body under the thyrotoxicosis (T4) effect.



FIGURE : Spleen: extensive hyperplasia of the white pulp in the periarterial sheath region (T –cell region) (→>) and hyperplasia of remainder region of white pulp (B-cell region) (→>)(200X H&E).



FIGURE 2: Heart: there is acute cellular swelling characterized by perinuclear vacuolated (), edema between muscle fibers (

Heart

Which grossly seen increased in size of the heart (hypertrophy) ,microscopically appeared as an acute cellular swelling in myocardial muscles fibers , and edema infiltrated between the muscle fibers in addition to increase cardiac movement cause hypertrophy in this study (Figure 12), this result agree with ^[28, 29, 20] and explain as a result hyperthyroidism increases total protein synthesis in cardiac myocytes, resulting in increased heart weight and a mild degree of cardiac hypertrophy and thyroid hormone stimulates myocyte hypertrophy, due to implicated changes in expression of myosin heavy chain (MHC) and sarcoplasmic reticulum Ca²⁺-ATPase ^{[30,31}].

Testis

More extensive lesions were observed in testicular tissue which appeared atrophied grossly and microscopically there was loss of spermatogenesis with hydropic degeneration of germinal layer lining seminiferous tubules and sloughing of their cell lining (Figure 13). Similar findings were observed by^[32] who found the high doses of thyroid hormone causes decrease in the weight of testis and seminal

vesicles in mice and rabbits seen in this study. Similarly ^[33] found that following thyrotoxicosis in rats the high level of thyroxine (T4) causes reduction in body and testis weights, reduction in testis weights in rats mainly result from reduction of total volume and the number of seminiferous tubules and loss of spermatogenesis in addition to the decrease in the interstitial mesenchymal cells (leydig cells) observed in this study.



FIGURE : Testis: loss of spermatogenesis (), sloughing and hydropic degeneration of their epithelial lining (), (200X H&E).



FIGURE : Uterus: there is extensive fibrous tissue formation in the subendometrial region (), with extensive collagen production () and reduction in endometrial gland and metaplasia of their epithelia lining () (200X H&E).

Uterus

endometrial metaplasia.

In this study the main lesion in this organ thickening of subendometrial layer due to over collagen production, fibroblast proliferation and reduced in number of endometrial glands (Figure 15), these findings were observed by ^[35] that this thickening of uterine wall (subendometrium) were result from action of thyroxine (T4) administration on the endometrium and myometrium and resulted into uterine wall thickness and affect the number of endometrial gland in addition to the

Ovaries

The main lesions in this organ, there is decrease in size (atrophied) grossly and microscopically there is reduces number and the size of the ovarian follicles, and increase in medullary region on expense of cortex (Figure 14). Hyperthyroidism in rats following T4 administration with a long period of time cause increase periods of diestrus with few follicles seen and extensive luteal tissue formation which observed in this study following T4 administration , these changes were accompanied by increase level of leuteinzing Hormone (LH), which associated luteal tissue formation ^[34] and decrease in Follicular – stimulating hormone (FSH) and Insulin like growth factor (IGF-1) concentration following thyrotoxicosis ^[35], these resulted into atrophy of ovary and small size follicle comparable to the normal control which was evident in this study.



FIGURE : Ovary: there is reducing in the number of growing follicle (), and extensive lutenization (luteal cell formation) (200X H&E).



FIGURE : Skin: extensive sclerosis with too much collagen production in dermal region () (200X H&E).

Skin

There is extensive sclerosis in the dermal region characterized by fibroblasts proliferation and too much collagen production (Figure 16). This results observed by ^{.37]} as result of that the skin is a classic target tissue for thyroid hormone action and thyroid hormone stimulate keratinocyte proliferation, also stimulated proliferation inhibitory factors from skin fibroblasts insight into the interplay among the competing factors will be important in understanding thyroid hormone regulation of skin physiology, and there was a dose-dependent of in thyroid

hormone (T3) treated animals increase in epidermal proliferation, dermal thickening, and hair growth in rats and mice and explain on the basis that proliferation-associated cytokeratin 6a expression and is dramatically stimulated with supraphysiologic doses of thyroid hormone . A similar findings recorded by ^[38, 39].

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