



Cairo University



**The ameliorating effect of melatonin  
hormone on the reproductive disorders and  
organ damage induced by hyperthyroidism  
in male rats**

*Thesis presented by*

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### Abstract

The present study was carried out to investigate the effects of melatonin on the reproductive disorder and organ damage induced by hyperthyroidism. A total 75 male rats were divided into five groups 15 rats each: control group (distilled water containing 4M ammonium hydroxide in methanol and 1% absolute ethanol), L-thyroxine group (0.2 mg/kg), L-thyroxine plus melatonin (1, 5 and 10 mg/ kg), L-thyroxine and melatonin were injected intraperitoneally daily for 21 days. Fasting blood samples were collected from each rat early in the morning at the 11th day and at the end of the experiment, serum was separated, fasting blood glucose level was measured immediately after serum collection and the serum stored either at -20 °C to be used for determination of liver function tests (AST, ALT and ALP), kidney function tests (creatinine level and urea concentration), lipogram (total cholesterol, triglycerides, HDL and LDL) and hormones (T4, T3, TSH, FSH, LH and testosterone) or at -80 °C for determination of total antioxidants capacity. Five rats were scarified from each group on the 11<sup>th</sup> day and at the end of the experiment and the following organs were collected to be used as follow liver, kidney and heart were used for estimation of oxidant and antioxidant parameters (MDA, SOD and GSH) while liver and kidney were used for determination of DNA damage and thyroid gland, Liver, kidney, heart and testis were used for histopathological examination at the end of experiment. The results revealed that hyperthyroidism increased the levels of glucose, urea, liver enzymes activities, T3, T4, testosterone, percentage of DNA fragmentation and MDA concentration with histopathological alteration. At the same time hyperthyroidism decreased the performance trait, creatinine, lipogram, TSH, LH, FSH, total antioxidants capacity, SOD and GSH activity. Melatonin hormone could counteract the harmful effects of hyperthyroidism on the aforementioned parameters but couldn't ameliorate the reproductive disorders.

**Key Words:** Melatonin- L-thyroxine- harmful effect- Ameliorating effect- Male rats.

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## *Dedication*

*To my family and husband to say  
thanks seems so small but, thanks  
for everything... their support,  
encouragement and helping me.*

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## LIST OF ABBREVIATION

| <b>Abbreviation</b> | <b>Complete words</b>            |
|---------------------|----------------------------------|
| <b>ALP</b>          | Alkaline phosphatase             |
| <b>ALT</b>          | Alanine aminotransferase         |
| <b>AP site</b>      | (A-purine or A-pyrimidine) site  |
| <b>AST</b>          | Aspartate aminotransferase       |
| <b>BER</b>          | Base-excision repair             |
| <b>BW</b>           | Body weight                      |
| <b>BWG</b>          | Body weight gain                 |
| <b>Camp</b>         | Cyclic adenosine monophosphate   |
| <b>CAT</b>          | Catalase                         |
| <b>CIH</b>          | chronic intermittent hypoxic     |
| <b>D1</b>           | Deiodinases type 1               |
| <b>D2</b>           | Deiodinases type 2               |
| <b>D3</b>           | Deiodinases type 3               |
| <b>DNA</b>          | Deoxyribonucleic acid            |
| <b>DPA</b>          | diphenylamine assay              |
| <b>EE</b>           | Entero-endocrine cell            |
| <b>FCR</b>          | Feed conversion ratio            |
| <b>FSH</b>          | Follicle stimulating hormone     |
| <b>GFR</b>          | Glomerular filtration rate       |
| <b>GGT</b>          | Gamma glutamyl-transferase       |
| <b>GH</b>           | Growth hormone                   |
| <b>GHRH</b>         | Growth hormone releasing hormone |

|                                |                                        |
|--------------------------------|----------------------------------------|
| <b>GIT</b>                     | Gastrointestinal tract                 |
| <b>GPx</b>                     | Glutathione peroxidase                 |
| <b>GSH</b>                     | Glutathione                            |
| <b>GST</b>                     | Glutathione-S-transferase              |
| <b>Hb</b>                      | Hemoglobin                             |
| <b>HCT</b>                     | Hematocrite                            |
| <b>HDL</b>                     | High density lipoprotein               |
| <b>HIOMT</b>                   | Hydroxyindole-O-methyl transferase     |
| <b>HPLC</b>                    | High performance liquid chromatography |
| <b>HT</b>                      | Hyperthyroidism                        |
| <b>I/P</b>                     | Intra-peritoneal                       |
| <b>IFN-<math>\alpha</math></b> | Interferon alpha                       |
| <b>IFN-<math>\gamma</math></b> | Interferon gamma                       |
| <b>IL- 10</b>                  | Interleukin 10                         |
| <b>IL-12</b>                   | Interleukin 12                         |
| <b>IL-2</b>                    | Interleukin 2                          |
| <b>IL-6</b>                    | Interleukin 6                          |
| <b>LBD</b>                     | Ligand-binding domain                  |
| <b>LBP</b>                     | Liver biochemical parameters           |
| <b>LDL</b>                     | Low density lipoprotein                |
| <b>LH</b>                      | Luteinizing hormone                    |
| <b>LPO</b>                     | Lipid peroxidation                     |
| <b>MCH</b>                     | Mean corpuscular hemoglobin            |
| <b>MCV</b>                     | Mean corpuscular volume                |

|             |                                  |
|-------------|----------------------------------|
| <b>MDA</b>  | Malondialdehyde                  |
| <b>MT1</b>  | Melatonin receptor 1             |
| <b>MT2</b>  | Melatonin receptor 2             |
| <b>NAT</b>  | Serotonin-N-acetyl transferase   |
| <b>NK</b>   | Natural killer cell              |
| <b>NO</b>   | Nitric oxide                     |
| <b>OH</b>   | Hydroxyl radical                 |
| <b>OS</b>   | Oxidative stress                 |
| <b>PVR</b>  | Peripheral vascular resistance   |
| <b>RBF</b>  | Renal blood flow                 |
| <b>RNS</b>  | Reactive nitrogen species        |
| <b>ROS</b>  | Reactive oxygen species          |
| <b>SC</b>   | Serum creatinine                 |
| <b>SCN</b>  | Suprachiasmatic nucleus          |
| <b>SHBG</b> | Steroid hormone binding globulin |
| <b>SOD</b>  | Superoxide dismutase             |
| <b>STC</b>  | Serum total cholesterol          |
| <b>SUN</b>  | Serum urea nitrogen              |
| <b>T3</b>   | Triiodothyronine                 |
| <b>T4</b>   | Thyroxine hormone                |
| <b>TAC</b>  | Total antioxidant Capacity       |
| <b>THR</b>  | Thyroid hormone receptor         |
| <b>THRa</b> | Thyroid hormone receptor-a       |
| <b>THRb</b> | Thyroid hormone receptor-b       |
| <b>TRH</b>  | Thyroid releasing hormone        |

|            |                             |
|------------|-----------------------------|
| <b>TSH</b> | Thyroid stimulating hormone |
|------------|-----------------------------|

## ***Chapter (1)***

### **INTRODUCTION**

## 1. INTRODUCTION

Thyroid hormones play a critical roles in cellular metabolism and regulate many pathways that are incorporated in the metabolism of carbohydrates, proteins and lipids in several tissues (**Cicatiello *et al.*, 2018**). Moreover, they are required for normal function of nearly all tissues, with main effects on oxygen consumption and metabolic rate (**Ma *et al.*, 2004**). In addition, thyroid hormones play an important role in the modulation of antioxidant systems and oxidative stress (**Mancini *et al.*, 2013**). Furthermore, they have a critical role in regulation and development of reproduction and testis function by controlling the function of Sertoli cells and Leydig cells (**Korejo *et al.*, 2016**), they are responsible for reproductive hormonal changes and alterations in development of the reproductive system (**Fadlalla *et al.*, 2017**). However, hyperthyroidism induces a hypermetabolic state characterized by increased resting energy loss, decreased cholesterol levels, increased lipolysis and gluconeogenesis followed by body weight loss (**Mullur *et al.*, 2014**). Hypermetabolic state in hyperthyroidism is associated with tissue oxidative damage and deterioration of antioxidant system (**Varghese *et al.*, 2001**). Furthermore, hyperthyroid tissue exhibit an increased reactive oxygen species and reactive nitrogen species production which cause severe oxidative damage nearly to all organs and affect their functions (**Venditti and Meo, 2006**).