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^{th} 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.

LIST OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATION

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

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

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

TSH	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).**