Original Article

The Role of Melatonin in Thyroid Function in Adult Rats

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ABSTRACT

Background: The thyroid gland, a vital endocrine organ, the thyroid gland synthesizes and secretes hormones, such as triiodothyronine (T3), thyroxine (T4), and calcitonin. The pineal gland produces and releases melatonin, which is stimulated in the dark and suppressed in the presence of light.

Objectives: This study aimed to assess how melatonin influences adult male rats' thyroid performance.

Methods: Eighteen adults male Wistar albino rats (*Rattus norvegicus*) (approximately 12-14 weeks old and weighing 220±10 g) were randomly divided into three groups, each containing six rats, and were treated for 30 days as follows: The control group (A) received distilled water (DW). The A1 group received 10 mg/kg body weight (B.W.) of melatonin orally daily, and the A2 group received 20 mg/kg B.W. of melatonin orally daily for 30 days. At the end of the study, blood was drawn by cardiac puncture, and serum was collected to assess thyroid hormone levels: T3, T4, thyroid stimulating hormone (TSH), and total antioxidant capacity (TAC).

Results: T3 levels increased dramatically in the A2 group, whereas T4 and TSH levels remained constant. On the other hand, there was a significant increase in TAC in the A1 groups compared with the control and A2-treated groups. The histological section of the thyroid glands revealed the normal histological structure of the thyroid in the A1 group compared to the A2 group. Besides, the figures of the thyroid gland in the A2 group showed severe vascular degeneration and necrosis of thyroid follicles.

Conclusion: Treatment with melatonin at higher doses may influence thyroid hormone regulation, highlighting its potential physiological effects, while melatonin at a dose of 10 mg/kg plays a key role in regulating thyroid functions and enhancing antioxidant status.

Keywords: Hormonal regulation, Oxidative stress, Pineal gland, Triiodothyronine (T3), Thyroxine (T4)

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Introduction

The thyroid gland, a vital endocrine organ, has two types of cells: follicular cells and C cells. The thyroid gland synthesizes and secretes hormones, such as triiodothyronine (T3), thyroxine (T4), and calcitonin (CT). These hormones play important roles in energy metabolism, substance metabolism, and growth and development (Yang et al., 2025). The pineal gland produces and releases melatonin and other peptides, such as noradrenaline (NE), via intraparenchymal nerve fibers. The release and activity of the pineal gland are stimulated in the dark and suppressed in the presence of light (Ross, 2024; Muayad et al., 2025).

Melatonin, often referred to as N-acetyl-5-methoxytryptamine, is the primary product of the pineal gland and is derived from serotonin with tryptophan as the precursor. It can also be found in a wide variety of plants, including legumes, pineapple, tomatoes, walnuts, olives, ginger, and cereals. It has a light-yellow stain and is highly soluble. Moreover, primarily regulates biological processes, including sleep and aging, through the circadian rhythm. It travels in plasma bound to proteins such as albumin.

Other melatonin sources identified by earlier studies included the gastrointestinal tract, blood lymphocytes, and the retina (de Albuquerque et al., 2020; Shalaby & Kashef, 2021). Melatonin plays several roles through specialized cell membrane receptors (MT1 & MT2), including regulating bone metabolism, ovarian follicle development, ovulation, luteinizing hormone, fertilization, implantation, and the circadian cycle of antioxidant enzymes (Megha et al., 2024). This hormone has antioxidant properties due to its small molecular size and lipolipid structure (Chainy & Sahoo, 2020). To prevent DNA damage, it may cross all cell membranes and enter intracellular compartments, such as the nucleus and mitochondria, which contain high levels of this hormone (Sousa Coelho et al., 2018).

Melatonin, a natural oncostatic hormone, has been shown to lessen the risk of developing cancer (Martínez-Campa et al., 2024). Furthermore, melatonin is regarded as a critical hormone that influences growth, development, maturation, and aging, with its plasma concentration decreasing as people age (Oyebanjo et al., 2024).

Although melatonin is widely recognized for its antioxidant and endocrine properties, the dose-dependent effects of melatonin on thyroid function remain insufficiently clarified. Previous studies have reported inconsistent findings, particularly regarding high-dose administration. Therefore, the present study aimed to evaluate the effects of two different doses of melatonin on thyroid function parameters in adult rats. We hypothesized that melatonin exerts a dose-dependent modulatory effect on thyroid activity, with moderate doses improving hormonal balance, while higher doses may induce paradoxical or inhibitory effects. The rationale for this study is based on the existing knowledge gap concerning the optimal therapeutic dose of melatonin and the potential for adverse or counter-regulatory responses at elevated concentrations.

Materials and Methods

Animal management

In the animal house of the Faculty of Veterinary Medicine at the University of Baghdad, all experimental procedures were reviewed and approved by the Ethics Committee of the College of Veterinary Medicine, University of Baghdad, Iraq. Adult male rats were obtained from the animal house of the College of Veterinary Medicine, Baghdad, in Iraq. The animals were housed in plastic cages with good ventilation, and they received continuous consumption of food and water during the study duration. A constant temperature of 22±2 ˚C was maintained, with a 12 h light/dark cycle for study and acclimation.

Experimental design

Eighteen male Wistar adult albino rats (*Rattus norvegicus*) (approximately 12-14 weeks old and weighing 220±10 g) were divided into three groups at random, each containing six rats, and given the following treatment for 30 days: the control (A) group received an oral gavage of 0.5 mL of distilled water (DW) only; the A1 group received an oral gavage of 10 mg/kg body weight (B.W.) of melatonin daily; and the A2 group received an oral gavage with 20 mg/kg B.W. of melatonin once daily for 30 days (Yousef et al., 2025).

Melatonin preparation

Melatonin was obtained from a local pharmacy in capsule form (10 mg per capsule; NOW®, USA). The capsules contained melatonin in powder form. The required amount of powder was suspended in DW and vortexed thoroughly to ensure homogeneity. The suspension was freshly prepared prior to administration. Melatonin was administered once daily in the evening at 6:00 pm to imitate the physiological circadian rhythm of melatonin

secretion. Rats were orally administered the prepared suspension by gavage, and the mixture was shaken immediately before each use to maintain uniform distribution of the active compound.

Sample collection

At the end of the experiment, a blood sample was drawn by cardiac puncture under general anesthesia. Sampling were performed in the light phase (between 9:00 and 10:00 am). Tissue samples were taken from euthanized animals and administered intramuscular injections of ketamine (90 mg/kg B.W.) and xylazine (40 mg/kg B.W.) (Kepro B.V., Holland/Netherlands) (Wellington et al., 2013). Serum was collected for examination of the following parameters: thyroid hormone levels (T3, T4, and thyroid stimulating hormone [TSH]). T3, T4, and TSH concentrations were measured according to the electrochemiluminescence immunoassay (ECLIA) using the COBAS INTEGRA e411 analyzer (Roche Diagnostics, Mannheim, Germany). Total antioxidant capacity (TAC) activity was measured using an enzymatic colorimetric kit (ab65329; Abcam, Cambridge, UK) (Silvestrini et al., 2023).

Histopathological analysis

A tissue sample from the thyroid gland was obtained and preserved in 10% neutral buffered formalin for histological analysis. The samples were processed according to standard histological procedures for preparing paraffin blocks and staining tissue sections using H&E stain (Bancroft & Layton, 2019).

Statistical analysis

The statistical analysis system (SAS, 2018) was used to determine the impact of various research parameters. One-way analysis of variance (ANOVA) was used to compare means in this study. The least significant difference (LSD) test was applied for post-hoc pairwise comparisons.

Results

Levels of thyroid gland hormones (T3, T4, and TSH)

Treatment of rats with melatonin administration showed a significant increase ($P \leq 0.05$) in T3 concentrations in the A2 group (treated with 20 mg melatonin) compared with the A1 and control groups. While T4 and TSH levels showed slight variation among groups, these differences were not statistically significant ($P < 0.05$) (Table 1).

TAC

Table 2 indicates a significant increase ($P \leq 0.05$) in TAC in the A1 group compared to the control and A2 groups, while the A2 group, which was treated with 20 mg of melatonin, did not show any significant differences compared to the control group.

Histopathological results

The histopathological changes in the control group showed normal histological structure of the thyroid gland, including normal appearance of follicles with normal follicular cells, C-cells, and colloid content (Figures 1 and 2). In the A1 group, the normal appearance of follicles with normal follicular cells, colloid, and capsule

Table 1. Effect of different melatonin doses on thyroid hormone levels (T3, T4, and TSH) in adult male rats

Groups	Mean±SE		
	T3 (ng/mL)	T4 (ng/mL)	TSH (mIU/L)
Control	0.62±0.06^{b}	59.66±5.65	0.017±0.008
A1	0.58±0.06^{b}	58.38±1.87	0.012±0.002
A2	0.82±0.07^{a}	70.96±5.61	0.022±0.006
LSD value	0.196*	14.565$^{\#}$	0.0184$^{\#}$
P	0.0449	0.159	0.515

$^{\#}$Non-significant, *Significant at $P \leq 0.05$.

Note: Means with different letters in the same column differed significantly. Mean± SE (n=6 for each group) are used to express values. A: control group rats receiving DW. A1: the group that received 10 mg/kg/B.W/daily of melatonin. A2: this group received 20 mg/kg/B.W of melatonin for 30 days.

Table 2. Effect of different melatonin doses on TAC in adult male rats

Groups	Mean±SE
	TAC (mmol/L)
Control	61.38±0.71[b]
A1	81.7±0.88[a]
A2	59.62±0.73[b]
LSD value	2.401**
P	0.0001

**Significant at P≤0.01.

Note: Means with different letters in the same column differed significantly. Mean± SE (n=6 for each group) are used to express values. A: control group rats receiving DW. A1: the group that received 10 mg/kg/B.W/daily of melatonin. A2: this group received 20 mg/kg/B.W of melatonin for 30 days.

in was observed (Figures 3 and 4). On the other hand, the A2 group showed severe vascular degeneration and necrosis of the thyroid follicles (Figures 5 and 6).

Discussion

This study demonstrates that the experimental administration of melatonin exerts dose-dependent effects on thyroid function, oxidative stress markers, and hormonal balance. A non-linear relationship between melatonin dosage and physiological outcomes was observed; while a 10 mg/kg dose significantly enhanced the antioxidant status within thyroid tissues and optimized glandular function, a higher dose of 20 mg/kg appeared to trigger a compensatory or unfavorable response, potentially suppressing thyroid hormone secretion. These findings highlight the therapeutic potential of moderate melatonin doses in modulating thyroid health and emphasize the necessity of precise dose titration to maximize efficacy while avoiding adverse endocrine disruptions (Garcia-Marin et al., 2015). Melatonin therapy improved thyroid activity in the treated groups; melatonin directly affects the thyroid gland, enhanced antioxidant capacity, and preserved normal thyroid architecture without altering hormone levels. Additionally, there is a strong correlation between the thyroid and pineal glands (İnkaya et al., 2025), indicating that thyroid dysfunction may impact melatonin production (Stępniak & Karbownik, 2024). Elevated T3 levels in group A2 showed, despite extensive tissue damage to the thyroid follicles, a seemingly paradoxical finding. This can be explained by two main possibilities. First, the elevated T3 may represent a compensatory response from the hypothalamic-pituitary-thyroid axis to try to maintain hormonal homeostasis after follicular damage, where overstimulation of the remaining follicular cells leads to transient over-secretion of the hormone. Second, the high

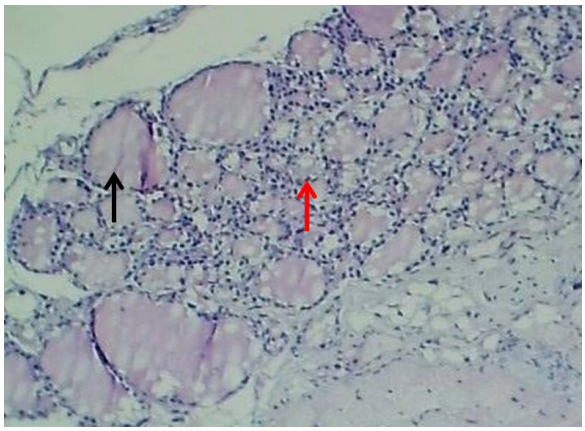

Figure 1. Section of the thyroid gland (control) showing normal appearance of large follicles (black arrows) and small follicles (red arrows) (H&E staining, 400x)

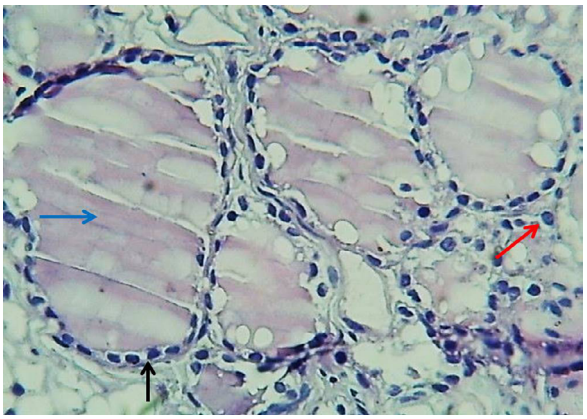

Figure 2. Section of the thyroid gland (control) showing normal appearance of follicles with normal follicular cells (black arrow), C-cells (red arrow), and colloid content (blue) (H&E staining, 400x)

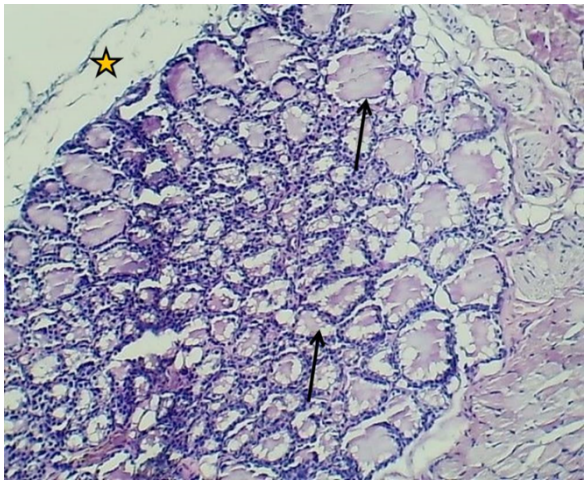

Figure 3. Section of the thyroid gland (A1) showing the normal appearance of follicles with normal follicular cells and colloid (arrows) and capsule (asterisk) (H&E staining, 400x)

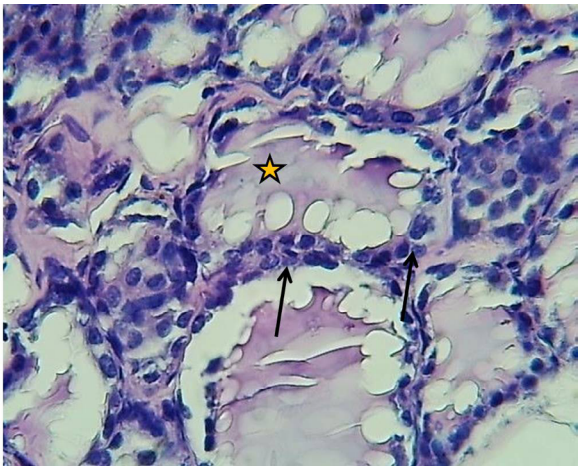

Figure 4. Section of the thyroid gland (A1) showing the normal appearance of follicles with normal follicular cells (arrows) and colloid (asterisk) (H&E staining, 400x)

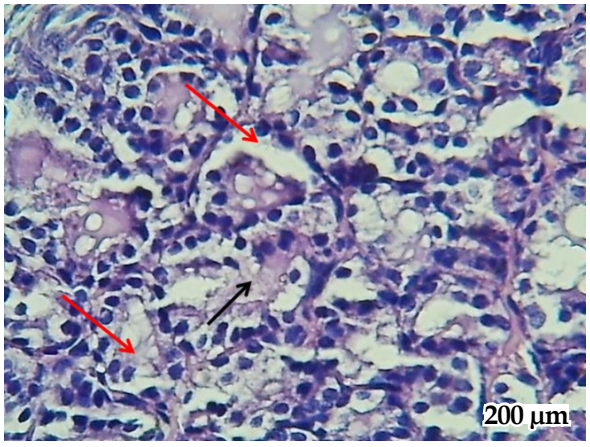

Figure 5. Section of the thyroid gland (A2) showing severe vascular degeneration (red arrows) and necrosis of thyroid follicles (black arrows) (H&E staining, 400x)

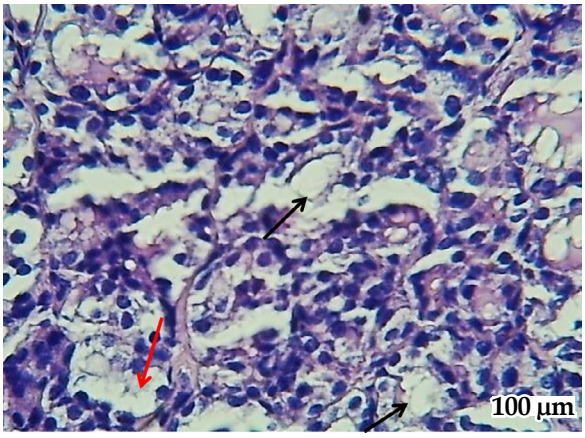

Figure 6. Section of the thyroid gland (A2) showing severe vascular degeneration (red arrows) and necrosis of thyroid follicles (black arrows) (H&E staining, 400x)

dose of melatonin may have produced a toxic or dysregulating effect. Some studies suggest that supraphysiological doses of melatonin may exhibit adverse oxidative effects or lead to desensitization/deregulation of MT1/MT2 receptors, causing a disruption in the TSH response and T3 secretion. Therefore, elevated T3 levels in group A2 does not reflect functional improvement, but is likely a compensatory response or a toxic effect of a high dose that resulted in dysregulation concurrent with the tissue damage (Salas-Lucia and Bianco, 2022).

Laskar et al. (2015) discovered that female rats' T4 levels rose when exposed to exogenous melatonin, suggesting that melatonin may influence thyroid hormone synthesis. However, in the present study, a significant increase was observed in T3 levels, rather than T4. This difference could be attributed to various factors, including the dose of melatonin used, the duration of treatment, and the physiological differences between male and female rats (Bakaa et al., 2023). Additionally, melatonin may enhance the conversion of T4 to T3 in peripheral tissues via deiodinase enzymes, leading to an increase in T3 levels without significantly affecting T4 concentrations (Alagbonsi et al., 2020). This suggests that melatonin's effect on thyroid hormones may be dose-dependent and influenced by specific metabolic pathways. The positive association between stromal and epithelial proportions and the negative correlation with colloid proportions demonstrated the relationship between melatonin and TSH levels (Yanko et al., 2020). Melatonin alone at high doses caused inhibition of thyroid activity and decreased hormone levels (Wright et al., 1996; Baltaci et al., 2004), suggesting that melatonin's effects are dose-dependent.

These results illustrated the antioxidative role of melatonin at normal doses, which increases TAC, and melatonin interacts with hydroxy radicals and counteracts their toxic effect (Al-Azawi et al., 2003; Sabeeh & Khudair, 2016; Ramadhan & Khudair, 2019). Also, it is suggested that melatonin is a well-known direct free radical scavenger and stimulates several antioxidative enzymes (Surour et al., 2022; Kouser et al., 2025). Supplementation of melatonin to the rats for 1-3 days decreased thyroid hormone levels, while 30 days of treatment caused an increase in thyroid hormone levels. Also, melatonin increases the activity of the thyroid gland due to its direct effect on thyroid hormone biosynthesis (Wang et al., 2024). In addition, melatonin may increase thyroglobulin expression and mRNA and protein levels, which affect thyroid activity (Öztürk et al., 2024). Histological research revealed that melatonin can decrease mitochondrial swelling and damage rat tissue (Mustafa et al., 2024). This suggests that melatonin may improve mitochondrial function, which directly affects the regulation of all intracellular reactions and thyroid function processing (Taher & Arrak, 2016). Melatonin has a thyroid protective effect (Ghavamikia et al., 2025).

One limitation of this study is that the histopathological assessment was qualitative rather than quantitative. Future studies may benefit from standardized assessment methods, blind assessment, and additional histochemical staining to further validate the observed histological changes. Despite the presence of degenerative changes in thyroid tissue, serum TSH levels remained normal. This apparent discrepancy may suggest that the histological changes were not extensive enough to elicit a compensatory hormonal response, or that TSH regulation involves additional factors beyond structural damage. Therefore, future studies using quantitative histopathology and functional testing are needed to clarify this relationship.

Conclusion

The findings demonstrate a dual and threshold-dependent effect of melatonin on thyroid function. While melatonin at 10 mg/kg exerted protective effects by improving antioxidant status and supporting thyroid regulation, the higher dose (20 mg/kg) was associated with structural damage and hormonal dysregulation, including altered T3 levels. These results suggest the existence of a critical dose threshold beyond which melatonin may shift from being protective to potentially harmful. Therefore, careful dose optimization is essential, and further studies are required to clarify the underlying mechanisms and long-term consequences of high-dose melatonin on thyroid homeostasis.

Ethical Considerations

Compliance with ethical guidelines

Acceptance was obtained under Approval No.: P.G. 857 because the procedures used in this study were examined and approved in accordance with animal welfare ethical standards by both the Ethics Committee of the College of Veterinary Medicine, University of Baghdad, Baghdad, Iraq, and the Scientific Committee of the Department of Physiology, Biochemistry, and Pharmacology, College of Veterinary Medicine, University of Baghdad, Iraq.

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Authors' contributions

Methodology and experiments: Muna Hasan Yousif; Data interpretation and statistical analysis: Jawad kadhim Arrak; Study design, supervision, review and editing: Sahib M. H. Mohammadbakir; Writing the original draft: Sadiq Jaffer Ramadhan.

Conflict of interest

The authors declared no conflict of interest.

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