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THE EXPERIMENTAL HYPOTHYROIDISM MODEL AND HEMATOLOGICAL RESULTS

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Abstract
In this study, the changes in hematological parameters of rats under an experimental hypothyroidism model were investigated. The research aimed to identify the disorders caused by thyroid hormone deficiency and to assess alterations in blood composition and immune system activity. Hypothyroidism was induced by oral administration of methimazole to rats for 30 days. The results showed that in the hypothyroid group (M±m, n=6), the number of red blood cells (RBC), hemoglobin (HGB), and hematocrit (HCT) levels significantly decreased compared to the control group. These findings indicate that thyroid hormone deficiency slows down hematopoiesis and reduces oxygen transport capacity. Additionally, an increase in the proportion of granulocytes suggested the activation of inflammatory processes, while elevated lymphocyte counts reflected an adaptive immune response. The enlargement of mean corpuscular volume (MCV) indicated the development of macrocytosis associated with impaired erythropoiesis. This study provides a reliable experimental basis for investigating hematological changes observed in hypothyroid conditions, allowing for the analysis of adaptive mechanisms in the blood system under endocrine

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dysfunction. The obtained results confirm that hypothyroidism leads to hematological imbalance and demonstrate a complex functional relationship between the blood and immune systems.

Keywords: Hypothyroidism, hematology, thyroid hormones, experimental model.

Introduction

Hypothyroidism is one of the most common endocrine disorders and represents one of the main research areas in modern experimental and clinical endocrinology. This condition arises due to insufficient synthesis of triiodothyronine (T3) and thyroxine (T4) hormones, leading to multisystem metabolic and morphological disorders (Chaulin et al., 2021). Thyroid hormones play a crucial role in regulating growth, energy metabolism, and neurophysiological processes; therefore, their deficiency causes serious functional changes in several body systems (Chaulin et al., 2021a).

Experimental induction of hypothyroidism in laboratory animals is considered an effective and ethically acceptable method for studying the pathophysiological mechanisms of this disorder and for evaluating therapeutic approaches before clinical application (Chaulin et al., 2020). Currently, several methods are used to induce hypothyroidism, including iodine deficiency, thyroidectomy, pharmacological inhibition (e.g., using methimazole or propylthiouracil), radioactive ablation, genetic modification, and immune-mediated suppression (Chaulin et al., 2021a). Among these, pharmacological induction using methimazole is recognized as the most widely applied, reversible, safe, and physiologically relevant model of human hypothyroidism.

Combining validated experimental models with biochemical and histopathological analyses allows for a deeper understanding of the systemic consequences of hypothyroidism. Consequently, this provides a strong scientific foundation for the development of new diagnostic and therapeutic strategies in endocrine research (Chaulin et al., 2021).

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Materials and Methods

The research was conducted at the Department of Human and Animal Physiology, National University of Uzbekistan, and in the laboratory of the Institute of Bioorganic Chemistry of the Academy of Sciences of the Republic of Uzbekistan. Male white rats weighing 180–200 g were kept in individual cages under natural light conditions with free access to food and water. Their diet included wheat, nuts, milk and dairy products, meat, vegetables, and greens to maintain metabolic stability. Before the experiment, the animals were acclimatized for two weeks at a temperature of 22–24°C and relative humidity of 40–60%.

Induction of Hypothyroidism

Hypothyroidism was induced using the method of Kozlov (2006) with slight modifications. Methimazole was administered orally to the rats at a dose of 5 mg per 200 g of body weight for 30 consecutive days. This protocol produced a chronic hypothyroid state, allowing for the investigation of long-term metabolic and morphological alterations. The effectiveness of the model was confirmed by a significant decrease in serum T3 and T4 hormone levels.

Alternative induction methods include the administration of methimazole in drinking water at a concentration of 0.025–0.1% for 21 days (Zhou et al., 2015); propylthiouracil (PTU) at a dose of 15 mg/kg by gavage for 45 days, or at 0.05% in drinking water for four weeks (Jassim et al., 2013; Salazar et al., 2017); surgical thyroidectomy (including artery/vein ligation and parathyroid reimplantation) (Xie et al., 2022; Pineda-Reynoso et al., 2010); and combined thyroidectomy with mercazolyl administration at 75 mg/kg for 14 days (Denefil & Charnosh, 2022).

To verify the hypothyroid condition, serum T3 and T4 levels (Kozlov, 2006), body weight, heart rate, rectal temperature, oxygen consumption (Denefil & Charnosh, 2022), and the histopathological structure of the thyroid gland were evaluated. This protocol provides a standardized model for morphophysiological studies of chronic hypothyroidism.

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Results and Discussion

Significant hematological changes were observed in the peripheral blood of rats under the experimental hypothyroidism model. Compared with the intact group, the number of red blood cells (RBC) in the hypothyroid group decreased from $8.31 \pm 0.82 \times 10^{12}$/L to $6.21 \pm 0.77 \times 10^{12}$/L, indicating suppression of the erythropoietic process. Similarly, hemoglobin (HGB) levels declined from 142 ± 5.2 g/L to 118 ± 7.2 g/L, while hematocrit (HCT) decreased from 0.53 ± 0.02 to 0.39 ± 0.03 ($p < 0.01$). These results correspond to the development of normocytic or hyperchromic anemia commonly observed in hypothyroid conditions.

The mean corpuscular volume (MCV) increased from 54.2 ± 4.0 fL to 56.8 ± 4.4 fL, reflecting compensatory morphological changes in erythrocytes. The reduction in erythropoiesis under hypothyroid conditions can be attributed to thyroxine (T_4) and triiodothyronine (T_3) deficiency, which leads to decreased bone marrow activity, reduced erythropoietin synthesis, and disrupted iron metabolism (Chaulin et al., 2021).

Leukocyte parameters also exhibited noticeable alterations. The percentage of granulocytes (Gran%) increased from $0.08 \pm 0.03\%$ to $0.55 \pm 0.03\%$ ($p < 0.001$), suggesting intensified inflammatory and oxidative stress processes. Lymphocyte count (Lym#) rose from $15.14 \pm 1.4 \times 10^9$/L to $17.04 \pm 1.1 \times 10^9$/L, which may indicate compensatory activation of the immune system.

The obtained findings are consistent with previous research. For example, Gomes et al. (2004) reported reduced erythrocyte and hemoglobin levels, as well as lymphocytosis, in hypothyroid rats, confirming that hypothyroidism affects not only metabolic but also immunohematological systems. The significant decrease in RBC count ($8.31 \pm 0.82 \rightarrow 6.21 \pm 0.77 \times 10^{12}$/L) observed in the hypothyroid group compared to the intact group indicates diminished hematopoietic activity. Likewise, Umezu et al. (1998) found that congenital hypothyroidism in rdw dwarf rats led to reduced bone marrow proliferation and suppressed erythropoiesis, resulting in anemia. The marked decline in hemoglobin concentration ($142 \pm 5.2 \rightarrow 118 \pm 7.2$ g/L) further supports that thyroid hormone deficiency slows down erythropoietic activity. *(Table 1)*

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Table 1. Hematological parameters of rats in the hypothyroidism model

Parameter	Intact (M ± m)	Hypothyroid (M ± m)	*p*-value
Gran %	0.08 ± 0.03	0.55 ± 0.03	***
Lym# ($\times 10^9$/L)	15.14 ± 1.4	17.04 ± 1.1	–
RBC ($\times 10^{12}$/L)	8.31 ± 0.82	6.21 ± 0.77	–
HGB (g/L)	142 ± 5.2	118 ± 7.2	*
HCT	0.53 ± 0.02	0.39 ± 0.03	**
MCV (fL)	54.2 ± 4.0	56.8 ± 4.4	–

*** $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (Student's *t*-test)**

Thyroid hormones play a crucial role in stimulating erythropoietin synthesis; their deficiency slows down the maturation and proliferation of blood cells in the bone marrow. These findings are consistent with the studies of Saba and Sayyadipoor (2019) and Ahmed and Mohammed (2020), who also reported a significant decrease in hemoglobin and hematocrit levels in hypothyroid conditions.

The reduction in HGB and HCT values, along with a slight increase in MCV, indicates the development of normocytic or macrocytic anemia. Dorgalaleh et al. (2013) observed a decline in hematological morphological parameters in hypothyroidism, accompanied by a relative increase in leukocyte and lymphocyte counts, reflecting a reactive immune response under thyroid hormone deficiency. In the hypothyroid group, alterations in white blood cell parameters were manifested by an increase in monocyte percentage during the third week and a rise in plateletcrit (PCT) percentage by the sixth week (Kandir et al., 2016). The rdw dwarf rat model also confirmed a significant reduction in hemoglobin and hematocrit levels (Umezu, Kagabu, Jiang, & Sato, 1998).

The increase in granulocyte and lymphocyte counts in hypothyroid rats reflects enhanced oxidative stress and inflammatory activation caused by thyroid hormone deficiency. Mancini et al. (2016) demonstrated that thyroid hormone deficiency elevates the secretion of proinflammatory cytokines (IL-6, TNF-α), enhances neutrophil activity, and alters both the number and function of lymphocytes, indicating adaptive immune responses aimed at maintaining internal homeostasis.

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The observed hematological alterations were time-dependent, showing greater intensity at the sixth week compared to the third week (Kandir et al., 2016), which suggests that prolonged hypothyroidism leads to progressive hematological dysfunctions. Nevertheless, since most parameters remained within physiological ranges, it can be inferred that compensatory mechanisms partially mitigated severe hematological disturbances.
The induction of hypothyroidism in rat models led to significant changes in hematological parameters. After six weeks of treatment, rats in the hypothyroid group showed a significant decrease in red blood cell count (RBC), hemoglobin concentration (HGB), and hematocrit percentage (HCT) compared to the euthyroid (healthy) control groups (Kandir, Sinan, & Keskin, 2016). These results were also confirmed by Shevtsova, Kozlov, and Novitskii (1994), who reported a reduction in erythrocyte and reticulocyte counts and a decrease in hemoglobin levels in hypothyroid animals (Shevtsova et al., 1994).
In an experimental hypothyroidism model using thyroidectomized rats, a significant decrease in β-adrenergic receptor binding sites on reticulocytes was observed. This finding indicates that thyroid hormones reduce their influence on the adenylate cyclase system of the cell membrane. As a result, oxygen transport through reticulocytes and the overall efficiency of the erythropoietic process decline (Stiles, Trujillo, & Scoggins, 1981).

Conclusion

The results of this study showed that experimental hypothyroidism causes profound functional changes in the red blood cell system. The observed decrease in the number of erythrocytes, hemoglobin concentration, and hematocrit percentage confirms that hypothyroidism suppresses the erythropoietic process and reduces the oxygen-carrying capacity of the blood. At the same time, the increase in the mean corpuscular volume (MCV) indicates the presence of compensatory changes within the erythrocyte population.
Analysis of the leukocyte formula showed an increase in the percentage of granulocytes and a slight rise in the number of lymphocytes in the hypothyroid

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group. These changes can be explained by mild inflammation and reactive activation of the immune system characteristic of hypothyroidism. The results indicate that thyroid hormones play an important role in maintaining hematopoietic balance, regulating not only erythropoiesis but also immunohematological control.

The obtained data provide an important experimental basis for understanding the pathogenesis of anemia associated with thyroid dysfunction and for developing new therapeutic approaches. The hypothyroidism model is recommended as a reliable experimental platform for studying bone marrow activity, the dynamics of blood cell elements, and immune system alterations. Future studies using this model aimed at investigating the interaction between oxidative stress, inflammatory markers, and erythropoietin signaling pathways will allow a deeper understanding of anemia associated with hypothyroidism.

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