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INTEGRATION OF THE HYPOTHALAMIC–PITUITARY–ADRENAL AND HYPOTHALAMIC–PITUITARY–THYROID AXES IN IMMUNOMETABOLIC ALLOSTASIS OF THE ACUTE PHASE OF INFLAMMATION: A UNIFIED CYTOKINE-MEDIATED REGULATORY COMPLEX

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Background. The acute phase of inflammation is accompanied by profound reprogramming of neuroendocrine regulation involving the Hypothalamic–Pituitary–Adrenal (HPA) and Hypothalamic–Pituitary–Thyroid (HPT) axes. Increased cortisol levels and decreased triiodothyronine reflect interconnected components of immunometabolic adaptation aimed at meeting the energy demands of innate immunity; however, the integration of systemic and tissue-level mechanisms underlying this response remains insufficiently defined.

Aim. To propose an integrative model of HPA–HPT axis interaction as a unified cytokine-mediated immunometabolic regulatory complex of the acute phase of inflammation, encompassing both systemic and cellular levels of regulation.

Materials and Methods. A narrative review of experimental, clinical, and review studies (1998–2025) indexed in PubMed, Scopus, ScienceDirect, EMBASE, MEDLINE, the Cochrane Library, and Google Scholar was conducted. The selection was based on the following keywords: low triiodothyronine syndrome, glucocorticoids, thyroid hormones, cytokines, phagocytes, immunometabolism. The research was conducted as a private initiative of the authors, without grant funding and state registration of the topic.

Research Ethics. Only those sources were selected for analysis whose authors clearly adhered to modern bioethical norms when conducting their research.

Results. During the acute phase of inflammation, coordinated activation of the HPA axis ensures mobilization of energy substrates, while remodeling of the HPT axis contributes to their functional redistribution in favor of effector mechanisms of innate immunity. Glucocorticoids modulate the intensity and spatial organization of the inflammatory response, whereas local action of thyroid hormones in phagocytes, particularly via deiodinase-dependent mechanisms, determines their metabolic phenotype and bactericidal activity. In this context, Low Triiodothyronine Syndrome (LT_3S) emerges as a component of adaptive immunometabolic reprogramming relevant to the phagocytic phase of inflammation. Disruption of coordination between the axes leads to allostatic overload.

Conclusions. Immunometabolic adaptation in the acute phase of inflammation is formed through the function of a unified cytokine-mediated regulatory complex involving the HPA and HPT axes at both systemic and cellular levels. LT_3S reflects not an isolated thyroid dysfunction but an adaptive redistribution of resources and regulation of immune function, including the bactericidal activity of phagocytes, supporting the need for integrative approaches to the assessment of neuroendocrine changes.

Keywords: *endocrinology, low triiodothyronine syndrome, glucocorticoids, thyroid hormones, phagocytes, immunometabolism.*

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Introduction

The organism's response to the acute phase of the inflammatory process is a complex integrated reaction involving interactions between the immune, endocrine, and metabolic systems. Under these conditions, functional stability is maintained not only by homeostatic mechanisms but also through dynamic reprogramming of regulatory processes, consistent with the concept of allostasis [1; 2]. A central role in this reprogramming is played by the Hypothalamic–Pituitary–Adrenal (HPA) and Hypothalamic–Pituitary–Thyroid (HPT) axes, which function as interconnected components of a unified neuroendocrine response [3–5].

During the acute phase of inflammation, activation of innate immunity is accompanied by increased production of proinflammatory cytokines (IL-1β, IL-6, TNF-α), which directly modulate the activity of neuroendocrine axes. Under their influence, the HPA axis is activated, leading to increased cortisol secretion, which ensures mobilization of energy substrates while simultaneously exerting immunoregulatory effects [3; 5; 7; 8]. Contemporary studies indicate that this response involves not only alterations in hormone secretion but also disturbances in hormone metabolism and tissue sensitivity, forming the basis of the concept of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) [6; 8; 9].

In parallel, remodeling of the HPT axis occurs, manifested by decreased triiodothyronine (T_3) levels in the absence of primary thyroid disease – a phenomenon known as Low Triiodothyronine Syndrome (LT_3S) [3; 10; 11]. These changes reflect a complex regulatory response involving both central suppression and tissue-specific modifications of Thyroid Hormone (TH) metabolism [4; 10; 11].

Traditionally, LT_3S has been regarded as an energy-conserving adaptive response. However, current evidence suggests that the combination of elevated cortisol levels and reduced circulating T_3 reflects a coordinated process of energy redistribution in favor of effector mechanisms of innate immunity [5; 10; 12–14]. In this context, not only systemic hormonal effects but also their local regulation in tissues become critically important. In particular, glucocorticoids modulate the intensity and direction of the inflammatory response through receptor-mediated mechanisms, whereas local TH metabolism determines the functional activity of immune cells [5; 11].

Despite significant advances in understanding the neuroendocrine response, most contemporary models analyze the HPA and HPT axes predominantly in isolation. This approach limits the understanding of their integrated role in the formation of immune-metabolic adaptation. In particular, mechanisms coordinating systemic and cellular levels of regulation, as well as the significance of local hormone action in innate immune cells, remain insufficiently elucidated. Therefore, the development of an integrative approach is warranted, in which the HPA and HPT axes are considered as a unified cytokine-mediated immunometabolic regulatory complex of the acute phase of inflammation.

Previous studies have formulated the concept of context-dependent thyroid adaptation and the immunometabolic role of LT_3S in the acute phase of inflammation [12–14], providing a foundation for further integrative analysis of neuroendocrine axis interactions. This approach allows interpretation of changes in cortisol and T_3 levels as a coordinated immunometabolic mechanism aimed at meeting the energy and functional demands of innate immunity.

Aim of study was to develop an integrative model of interaction between the HPA and

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HPT axes in the acute phase of inflammation as a unified cytokine-mediated immunometabolic regulatory complex, taking into account both systemic and cellular levels of regulation.

Materials and Methods

A narrative analysis of contemporary experimental, clinical, and review studies addressing neuroendocrine regulation of the immune response, immunometabolic adaptation, the role of glucocorticoids and thyroid hormones in the acute phase of inflammation, and the pathophysiology of LT_3S was conducted.

The analysis included publications from 1998 to 2025 indexed in PubMed, Scopus, ScienceDirect, EMBASE, MEDLINE, the Cochrane Library, and Google Scholar. Sources were selected using the following keywords: low triiodothyronine syndrome, glucocorticoids, thyroid hormones, cytokines, phagocytes, immunometabolism. Full-text articles in Ukrainian and English were included in the analysis. Conceptual framework of the study was an unified cytokine-mediated immunometabolic regulatory complex of the HPA–HPT axes in the acute phase of inflammation.

This study proposes the concept of immunometabolic allostasis, in which neuroendocrine regulation during the acute phase of inflammation is considered as a unified cytokine-mediated immunometabolic regulatory complex functioning under the predominant influence of cytokine signaling.

A key premise of this model is the interpretation of the HPA and HPT axes as interconnected regulatory circuits, whose coordinated activity ensures redistribution of energy resources in favor of effector mechanisms of innate immunity. Within this framework, increased cortisol levels are viewed as a mechanism for mobilization of energy substrates and control of the inflammatory response, whereas decreased T_3 levels are interpreted as a mechanism for limiting energy consumption in non-critical tissues and optimizing resource utilization by immune cells.

Importantly, the model incorporates the cellular level of regulation: the local action of glucocorticoids and thyroid hormones in phagocytes determines their metabolic activity, bactericidal function, and the balance of cytokine responses. Thus, the proposed model considers neuroendocrine changes not as isolated phenomena but as a coordinated immunometabolic mechanism of adaptation.

For the purposes of this model, a unified cytokine-mediated regulatory complex is defined as a functional network in which proinflammatory cytokines (IL-1β, IL-6, TNF-α) simultaneously modulate HPA axis activation (increased cortisol) and HPT axis remodeling (decreased T3, increased rT3, altered deiodinase activity), with these hormonal changes being statistically and temporally linked to specific phases of the inflammatory response (initiation, amplification, resolution).

Research Ethics

Only those sources whose authors clearly adhered to modern bioethical norms when conducting their research were selected for analysis.

Results

1. Theoretical foundations: allostasis and cytokine-mediated regulatory reprogramming

1.1. From homeostasis to allostasis: a shift in the regulatory paradigm

The classical concept of homeostasis implies maintenance of internal stability through preservation of constant physiological parameters. However, during the acute phase of inflammation, this model is insufficient to explain systemic adaptive changes. Contemporary understanding is based on the concept of allostasis, according to which stability is achieved through dynamic reprogramming of regulatory mechanisms depending on the organism's needs [1; 2; 15].

Within the allostatic model, neuroendocrine axes do not maintain a fixed set point but instead adjust it in response to stressors, including inflammation. This is accompanied by reorganization of feedback mechanisms, alterations in receptor sensitivity, and redistribution of functional priorities among physiological systems. Thus, allostasis reflects a transition from maintenance of equilibrium to active adaptation aimed at ensuring survival [1; 2; 15].

1.2. Cytokines as integrators of the neuroendocrine response

During the acute phase of inflammation, proinflammatory cytokines –particularly IL-1β,

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IL-6, and TNF-α – play a key role in coordinating the adaptive response. They function not only as effectors of the immune response but also as central regulatory signals integrating immune and endocrine systems [4; 16; 17].

Under the influence of cytokine signaling, neuroendocrine regulation is reprogrammed at all levels: hypothalamic function is modulated, pituitary hormone secretion is altered, and the activity of peripheral endocrine organs is reorganized. As a result, a new regulatory circuit is formed in which cytokine-mediated mechanisms partially replace classical neurotransmitter pathways of control [16; 17]. This shift ensures coordinated activation of the HPA axis along with simultaneous remodeling of the HPT axis, collectively forming an integrated neuroendocrine response to inflammatory stress [4; 16].

Thus, proinflammatory cytokines act not only as triggers of the neuroendocrine response but also as mechanisms of functional integration of the HPA and HPT axes within a unified regulatory complex of the acute phase.

1.3. Immunometabolic allostasis as a model of acute-phase adaptation

During the acute phase of inflammation, allostatic reprogramming acquires an immunometabolic character, as neuroendocrine regulation becomes oriented toward meeting the metabolic demands of the immune system [12–14; 17; 18]. As a result of coordinated activation of the HPA axis and remodeling of the HPT axis, an integrated immunometabolic network is formed.

Activation of the HPA axis ensures mobilization of energy substrates through induction of proteolysis, lipolysis, and gluconeogenesis, while also modulating the intensity of the immune response [5; 19; 20]. In parallel, remodeling of the HPT axis – characterized by decreased circulating T_3 levels and alterations in deiodinase activity – limits energy consumption in peripheral tissues and promotes redistribution of resources toward effector mechanisms of innate immunity [3; 10; 11; 21].

As a result, systemic redistribution of energy occurs: tissues not critical for immediate survival shift toward a catabolic state, enabling the release of energy substrates required to support functional activity of immune cells [12; 13; 17; 18].

This approach further develops the previously proposed concept of context-dependent thyroid adaptation and the immunometabolic role of LT_3S in the acute phase of inflammation [12–14], extending it by incorporating the integration of the HPA and HPT axes into a unified cytokine-mediated regulatory circuit.

At the cellular level, this interaction is realized through metabolic reprogramming of immune cells. Glucocorticoids modulate the intensity and direction of the inflammatory response by influencing macrophage and neutrophil function, including phagocytosis and production of reactive oxygen species [5; 19; 20]. At the same time, thyroid hormones, through local metabolism, determine the cellular energy phenotype and bactericidal activity [11; 21; 23].

Thus, immunometabolic allostasis in the acute phase of inflammation should be considered a coordinated multilevel mechanism integrating neuroendocrine regulation, metabolic reprogramming, and effector functions of innate immunity [12–14; 17; 18].

1.4. Disruption of Coordination and Transition to Dysregulation

Under conditions of prolonged or excessive inflammatory burden, the coordinated interaction between the HPA and HPT axes may become disrupted. This is accompanied by reduced efficiency of glucocorticoid signaling, alterations in thyroid metabolism, and the development of a state of relative hormonal resistance [6; 8; 9].

In such conditions, even normal or elevated cortisol levels may fail to produce an adequate biological effect, reflecting the development of immunometabolic dysregulation. Impaired coordination between neuroendocrine axes determines the severity of the clinical course and underlies the transition from adaptation to allostatic overload [6; 8; 9; 22].

This indicates that the boundary between adaptation and dysregulation is determined by the efficiency of coordination between neuroendocrine axes and the system's ability to maintain an integrated response to inflammatory stress, as summarized in *Figure 1*.

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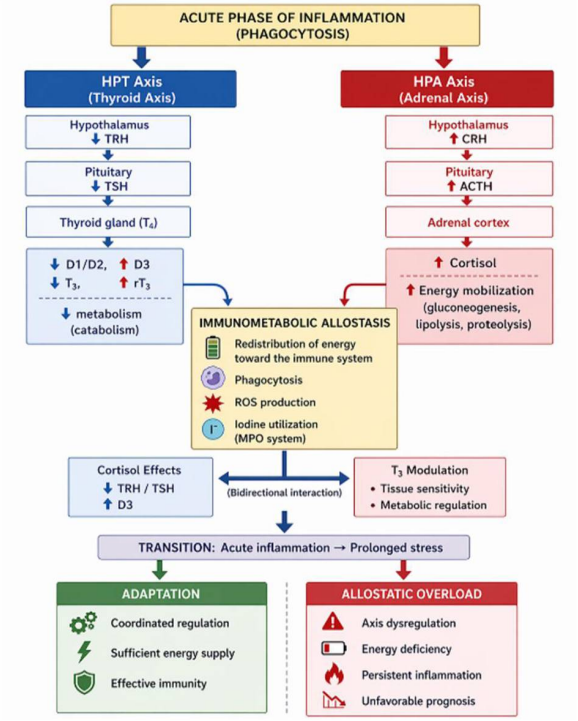

Fig. 1. Integrative model of immunometabolic allostasis in the acute phase of inflammation

Notes:

ACTH – adrenocorticotropic hormone;
CRH – corticotropin-releasing hormone;
D1/D2 – deiodinases type 1 and 2;
D3 – deiodinase type 3;
HPA – hypothalamic-pituitary-adrenal axis;
HPT – hypothalamic-pituitary-thyroid axis;
LT3S – low T3 syndrome;
MPO – myeloperoxidase;
ROS – reactive oxygen species;
rT_3 – reverse triiodothyronine (reverse T_3);
T_3 – triiodothyronine;
T_4 – thyroxine;
TRH – thyrotropin-releasing hormone;
TSH – thyroid-stimulating hormone.

The diagram illustrates the coordinated activation of HPA axis and remodeling of HPT axis as a mechanism of allostatic adaptation. Increased cortisol levels ensure mobilization of energy resources, whereas decreased T_3 promotes their redistribution in favor of the immune system. At the cellular level, hormones modulate immune cell functions, including phagocytosis and bactericidal activity. Disruption of this coordination leads to allostatic overload.

2. The HPA axis in the acute phase of inflammation: resource mobilization and control of inflammation

2.1. Cytokine-induced activation of the HPA axis

During the acute phase of inflammation, activation of the HPA axis represents a key component of the systemic adaptive response. Unlike the classical stress response, its activation in this context is largely initiated by proinflammatory cytokines, particularly IL-1β, IL-6, and TNF-α, which act as central triggers of neuroendocrine reprogramming [4; 16; 24].

Cytokines stimulate the secretion of corticotropin-releasing hormone (CRH) in the hypothalamus, leading to the release of adrenocorticotropic hormone (ACTH) from the pituitary and subsequent cortisol secretion by the adrenal cortex [4; 24; 25]. In addition to central activation, cytokines may directly affect the adrenal cortex, modulating steroidogenesis and altering the sensitivity of peripheral components of the axis [20; 24]. Signal transmission from the peripheral site of inflammation to central structures occurs via both humoral pathways and afferent neural mechanisms, including the *vagus* nerve, ensuring rapid integration of immune and neuroendocrine responses [24; 26].

As a result, the HPA axis functions not only as a classical stress system but also as an integrator and effector of the inflammatory response. Its activation is accompanied by reorganization of feedback mechanisms, changes in glucocorticoid sensitivity, and a shift from relatively stable homeostatic regulation to a dynamic allostatic mode [4; 15; 24].

2.2. Glucocorticoids as regulators of the immune response

Glucocorticoids are the principal effector hormones of the HPA axis, mediating its integrative influence on the immune system. Contemporary concepts emphasize that their role extends beyond simple suppression of inflammation to fine-tuned regulation of its intensity, spatial organization, and temporal dynamics [5; 19; 20].

At the level of innate immunity, glucocorticoids modulate macrophage and neutrophil function, influencing cytokine production, phagocytosis, reactive oxygen species generation, cell survival, and the rate of resolution [5; 19; 20]. They also regulate the expression of adhesion molecules, vascular permeability, and leukocyte migration, thereby limiting

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excessive tissue infiltration and secondary damage [19].

Within adaptive immunity, glucocorticoids influence the functional polarization of T lymphocytes, including modulation of the Th1/Th2 balance and suppression of excessive cytotoxic and proinflammatory activity [5]. Therefore, their action should be considered immunomodulatory rather than purely immunosuppressive. Importantly, these effects are phase-dependent: in early stages they restrain hyperactivation of inflammation, whereas in later stages they promote resolution and tissue repair [5; 20].

2.3. Metabolic effects: catabolism and substrate mobilization

In addition to their immunoregulatory function, glucocorticoids play a key role in the metabolic reprogramming of the organism during inflammation. They induce catabolic processes aimed at mobilizing energy substrates required to support the effector functions of the immune system [18–20].

The principal mechanisms include proteolysis in skeletal muscle with the release of amino acids, lipolysis in adipose tissue with the generation of free fatty acids, and hepatic gluconeogenesis, which ensures the maintenance of glucose availability for cells with high energy demands [18–20]. An important component of this metabolic adaptation is that, under conditions of systemic inflammation, the effects of glucocorticoids are accompanied by the development of relative insulin resistance and so-called "stress-induced" or "inflammatory" hyperglycemia, also referred to as "surgical diabetes". In this context, hyperglycemia should be interpreted not merely as a metabolic disturbance, but as a component of the adaptive response that ensures increased glucose availability for innate immune cells. Elevated circulating glucose levels facilitate its enhanced uptake by immune cells, whose metabolic activity largely depends on glycolytic pathways that support phagocytosis, Reactive Oxygen Species (ROS) production, and other effector functions. As a result, tissues that are not critical for immediate survival shift toward an energy-donor mode, whereas the immune system gains priority access to metabolic substrates.

Such redistribution of resources is consistent with the concept of immunometabolic adaptation and with previously proposed views of LT_3S as a component of systemic energy redistribution in favor of innate immune effector mechanisms [12–14; 17; 18]. In this context, activation of the HPA axis ensures substrate mobilization, while concurrent thyroidal reprogramming promotes their targeted utilization.

At the same time, glucocorticoids influence not only substrate metabolism but also mitochondrial function and cellular redox balance, which determine the efficiency of energy metabolism and the adaptive potential of tissues [20]. Thus, the HPA axis should be regarded not merely as a source of hormonal response to inflammation, but as a central mechanism of metabolic mobilization.

2.4. Dysregulation of the HPA axis in severe inflammation

Under conditions of severe or prolonged inflammation, the adaptive role of the HPA axis may transition into a state of dysregulation. One of the key manifestations is Critical Illness-Related Corticosteroid Insufficiency (CIRCI), characterized by disturbances in glucocorticoid secretion, metabolism, and tissue responsiveness. In contemporary understanding, CIRCI does not represent a simple cortisol deficiency but reflects a complex immunoendocrine dysregulation involving central, peripheral, and receptor-level mechanisms [6; 8; 9].

A crucial component of this condition is the development of glucocorticoid resistance, in which even normal or elevated cortisol levels fail to produce an adequate biological response [9; 20]. This is associated with alterations in receptor expression and function, post-receptor signaling pathways, and local hormone metabolism within tissues [6; 8; 9].

In addition, critical illness is associated with loss of circadian and ultradian rhythmicity of cortisol secretion, leading to desynchronization of regulatory processes and reduced effectiveness of hormonal responses [25]. Collectively, these changes reflect a transition from adaptive activation to immunometabolic dysregulation, which is associated with severe disease course and unfavorable prognosis [6; 8; 9].

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Clinical data confirm the key role of the HPA axis in maintaining adaptation during severe inflammation. Administration of glucocorticoids in sepsis is associated with improved hemodynamics and reduced vasopressor requirements; however, their effect on survival remains context-dependent [7; 27; 28]. A similar phase-dependent effect has been demonstrated in COVID-19, where the clinical benefit of corticosteroids depends significantly on disease severity and the stage of the inflammatory process [29].

These findings indicate that the functional state of the HPA axis is one of the critical determinants of the boundary between effective adaptation and allostatic overload. Thus, in the acute phase of inflammation, the HPA axis exerts its adaptive function not in isolation but as part of a unified cytokine-mediated immunometabolic regulatory complex.

3. The HPT axis in the acute phase of inflammation: thyroid reprogramming and energy redistribution

3.1. LT_3S as a component of inflammatory allostasis and central–peripheral remodeling of the HPT axis

Remodeling of the HPT axis in the acute phase of inflammation has traditionally been described within the framework of NTIS, the most typical manifestation of which is LT_3S [3; 10; 11; 22]. However, current evidence suggests that these changes should not be regarded as an isolated thyroid dysfunction but rather as a component of inflammatory allostasis, in which regulatory control shifts from classical neuroendocrine mechanisms toward cytokine-mediated coordination of immune and metabolic responses [4; 11; 15; 16].

Proinflammatory cytokines, particularly IL-1β, IL-6, and TNF-α, affect all levels of the HPT axis: they suppress hypothalamic expression of thyrotropin-releasing hormone (TRH), reduce pituitary secretion of thyroid-stimulating hormone (TSH), and simultaneously alter peripheral TH metabolism [3; 10; 16]. As a result, a new regulatory set point is established, in which the thyroid system becomes integrated into the immune response program.

A key mechanism underlying this remodeling is the alteration in deiodinase activity. During inflammation, the activity of type 1 and type 2 deiodinases (D1 and D2) decreases, while type 3 deiodinase (D3) is induced, leading to inactivation of TH and increased production of reverse T_3 (rT_3), thereby reducing systemic levels of biologically active T_3 [10; 11; 21]. Importantly, these changes are highly tissue-specific and reflect local metabolic demands.

Thus, LT_3S in the acute phase of inflammation represents not merely a laboratory finding but the result of coordinated central–peripheral remodeling of the HPT axis integrated into the system of inflammatory allostasis.

3.2. Systemic reduction of T_3 and energetic "reprogramming"

Systemic reduction of T_3 levels during acute inflammation has long been interpreted as an energy-conserving mechanism. However, current concepts indicate that this response is more complex and reflects active redistribution of energy resources according to the needs of the immune system [12–14; 17; 18].

Reduced thyroid activity limits energy consumption in tissues that are not critical for immediate survival, such as skeletal muscle and adipose tissue. At the same time, these tissues shift toward a catabolic state and become sources of amino acids, fatty acids, and glucose required to sustain energy-demanding processes of innate immunity, including phagocytosis and reactive oxygen species production [17–20].

In this context, thyroid remodeling is functionally coordinated with HPA axis activation: glucocorticoids ensure mobilization of energy substrates, whereas reduced T_3 promotes their more selective and efficient utilization [4; 5; 12–14].

Therefore, thyroid adaptation in the acute phase of inflammation reflects not passive energy conservation but active energetic "reprogramming" of the organism. From this perspective, LT_3S should be regarded as a key component of immunometabolic allostasis rather than merely a marker of disease severity.

3.3. Local thyroid regulation in immune cells

A fundamentally important aspect of the modern understanding of LT_3S is the recognition that systemic TH levels do not adequately reflect their local action within tissues, particularly in innate immune cells [11; 21].

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Against the background of systemic reduction in thyroid activity, local reprogramming of thyroid signaling occurs. Notably, type 3 Deiodinase (D3) is expressed in neutrophils and localized within bactericidal granules, where it plays a key role in antimicrobial function and reactive oxygen species production [23]. In macrophages, TH regulate cellular metabolic phenotype, activation status, and effector function [21].

Thus, cytokines exert a dual effect: on the one hand, they suppress systemic thyroid regulation, and on the other, they reprogram local TH action according to the needs of the immune response. This ensures tissue-specific optimization of energy metabolism and immune cell effector functions.

3.4. The HPT axis as an energetic component of immunometabolic coordination

Systemic and local remodeling of the HPT axis establishes a multilevel regulatory strategy that combines restriction of energy consumption with its targeted redistribution. This dual strategy–systemic reduction of thyroid activity alongside local metabolic reprogramming–creates optimal conditions for an effective immune response.

Functionally, the HPT axis closely interacts with the HPA axis: glucocorticoids ensure mobilization of resources, whereas thyroid remodeling promotes their rational utilization and distribution among tissues [4; 5; 12–14]. Together, these systems form an integrated immunometabolic network that supports phagocytosis, reactive oxygen species production, and other effector mechanisms of innate immunity [17; 18; 21].

Thus, the HPT axis in the acute phase of inflammation should not be viewed as a passively suppressed system but rather as an active regulator of energy balance and cellular functional activity. Its remodeling is an integral component of immunometabolic allostasis and determines the effectiveness of the adaptive response.

In summary, remodeling of the HPT axis in acute systemic inflammation represents a complex multilevel process involving central suppression, alterations in deiodinase activity, and tissue-specific modification of hormonal signaling. These changes reflect not dysfunction but an adaptive strategy aimed at redistribution of energy resources and support of the immune response. In interaction with the HPA axis, the thyroid system forms an integrated regulatory network underlying immunometabolic allostasis. Therefore, HPT axis remodeling should be regarded not as an autonomous thyroid response but as a component of a unified cytokine-mediated regulatory complex coordinating immunometabolic adaptation in the acute phase of inflammation.

4. Crosstalk between the HPA and HPT axes: integration of endocrine systems in the regulation of immunometabolic allostasis

Remodeling of the HPT axis during the acute phase of inflammation, as described in the previous section, occurs in close functional interaction with the HPA axis. Together, these axes form an integrated neuroendocrine–immune system in which hormonal and cytokine signals are coordinated to ensure adaptation to inflammatory stress [4; 16; 30].

4.1. Integration of the HPA and HPT axes in inflammatory allostasis

Under physiological conditions, regulation of the HPA and HPT axes is primarily mediated by neuroendocrine mechanisms with well-organized negative feedback loops. However, during the acute phase of inflammation, a fundamental shift in the regulatory paradigm occurs: proinflammatory cytokines – particularly IL-1β, IL-6, and TNF-α – assume a leading role as central integrators of the neuroendocrine response [4; 16; 24].

Cytokines simultaneously activate the HPA axis through stimulation of CRH and ACTH secretion and suppress the HPT axis at the levels of the hypothalamus, pituitary, and peripheral tissues [3; 10; 31]. In parallel, glucocorticoids released as a result of HPA activation further modulate thyroid regulation by inhibiting TRH and TSH secretion and influencing TH metabolism via deiodinases [5; 11; 31].

Thus, the HPA and HPT axes function as interconnected components of a unified system in which cytokine-mediated regulation partially replaces classical neurotransmitter-driven homeostatic control and ensures coordinated adaptation to inflammatory stress [17; 18].

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4.2. Immunometabolic reprogramming and the role of tissue-level regulation

The coordinated interaction between the HPA and HPT axes forms the basis of immunometabolic reprogramming. Glucocorticoids ensure mobilization of energy substrates through activation of proteolysis, lipolysis, and gluconeogenesis, whereas remodeling of thyroid signaling promotes redistribution of energy fluxes and optimization of their utilization [18–20].

In this context, systemic reduction of thyroid activity limits energy consumption in tissues not essential for immediate survival, such as skeletal muscle and adipose tissue, which simultaneously serve as sources of endogenous energy substrates. This is accompanied by a shift of these tissues into a catabolic state and mobilization of resources to support energy-demanding processes of innate immunity [3; 10; 11].

At the same time, local metabolic reprogramming occurs at the level of immune cells, regulated by TH and deiodinases, particularly D3 [21; 23; 32]. This ensures efficient phagocytosis, production of reactive oxygen species (ROS), and other effector functions, largely independent of systemic hormone levels.

Thus, immunometabolic adaptation is achieved through a combination of systemic energy redistribution and tissue-specific regulation coordinated by the interaction between the HPA and HPT axes [12–14; 17; 18].

4.3. Functional integration: resource mobilization and redistribution

Functional interaction between the HPA and HPT axes is realized through coordination of two complementary processes – mobilization and redistribution of energy resources.

Activation of the HPA axis, accompanied by increased cortisol levels, ensures substrate mobilization via induction of proteolysis, lipolysis, and gluconeogenesis [18–20], while simultaneously creating metabolic conditions for their redistribution. In parallel, reduced T_3 levels limit energy consumption in peripheral tissues and promote redirection of resources toward the immune system [3; 10; 11].

Thus, thyroid remodeling is not merely an energy-conserving response but serves to optimize the utilization of mobilized resources. Together, these processes form an integrated immunometabolic network in which mobilization and targeted energy utilization are functionally interconnected [17; 18].

4.4. Transition from adaptation to allostatic overload

During the acute phase of inflammation, integration of the HPA and HPT axes is adaptive and supports survival. However, prolonged, excessive, or dysregulated activation of these mechanisms leads to allostatic overload.

This state is characterized by persistent hyperactivation of the HPA axis, suppression of the HPT axis, loss of hormonal rhythmicity, progressive catabolism, and immune dysfunction, all of which are associated with adverse clinical outcomes in critical illness [6; 8; 9; 22; 25; 33].

Under such conditions, crosstalk between endocrine axes shifts from an adaptive mechanism to a pathophysiological process. This underscores that the effectiveness of the hormonal response is determined not only by the levels of individual hormones but by the preservation of coordination between regulatory systems.

4.5. Concept of a unified thyroid-adrenal regulatory complex

The presented data support the view that the HPA and HPT axes should be considered components of a unified cytokine-mediated thyroid–adrenal immunometabolic regulatory complex, within which integration of immune, endocrine, and metabolic responses is achieved.

A key feature of this complex is functional complementarity: glucocorticoids ensure mobilization of energy resources and control of inflammatory intensity, whereas thyroid remodeling determines the efficiency of their utilization and cellular metabolic reprogramming [5; 11; 20; 21; 32].

Importantly, the effectiveness of the hormonal response is determined not so much by circulating levels of cortisol and T_3 as by their tissue-level implementation, regulated by local enzymatic mechanisms – 11β-hydroxysteroid dehydrogenases for glucocorticoids and deiodinases for TH [11; 21; 33]. In this context, not only hormone levels but also preservation

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of their temporal dynamics, receptor sensitivity, and metabolic context of action are critical.

Disruption of this integration leads to loss of coordination between mobilization, redistribution, and utilization of energy resources, which underlies allostatic overload and limits the effectiveness of isolated therapeutic approaches.

Thus, the HPA and HPT axes should be regarded as a unified thyroid–adrenal regulatory circuit in which hormonal signals are implemented through multilevel coordination of systemic and tissue-specific mechanisms. This integration forms the functional basis of immunometabolic allostasis – an adaptive strategy that aligns immune responses with the organism's metabolic resources.

5. Immunometabolic allostasis: an integrative model of HPA–HPT interaction

The mechanisms discussed above indicate that interaction between the HPA and HPT axes in the acute phase of inflammation cannot be reduced to parallel endocrine changes but instead forms a unified cytokine-mediated immunometabolic regulatory complex of the acute phase of inflammation [4; 16; 30].

Within this system, hormonal and cytokine signals coordinate not only the nature of metabolic reprogramming but also the prioritization of energy resource utilization, the functional state of immune cells, and the temporal organization of the adaptive response. In this context, LT_3S should be regarded as a component of a unified immunometabolic network rather than an isolated thyroid abnormality [3; 10; 31].

A schematic representation of this HPA–HPT integration is presented in *Figure 2*.

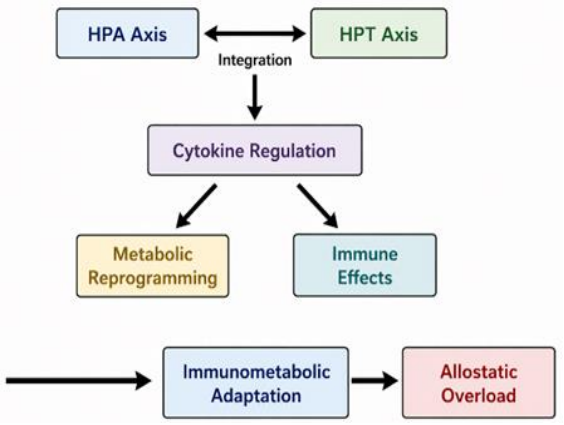

Fig. 2. HPA–HPT integration in immunometabolic allostasis

The model illustrates coordinated activation of the HPA axis and suppression of the HPT axis as a unified adaptive response. Glucocorticoids ensure mobilization of energy resources and regulation of inflammation, whereas changes in thyroid signaling promote redistribution of energy consumption and support immune cell metabolism. Cytokines integrate endocrine and immune signaling pathways, enabling metabolic reprogramming, reactive oxygen species production, and spatial organization of the immune response. Disruption of this coordination contributes to the development of allostatic overload.

5.1. Systemic redistribution of energy resources

Within the framework of immunometabolic allostasis, the key feature is not a reduction in energy expenditure *per se*, but its hierarchical redistribution according to the needs of innate immunity. HPA-mediated substrate mobilization and HPT-mediated limitation of energy consumption in peripheral tissues form a coordinated response in which skeletal muscle, adipose tissue, and the liver are reoriented toward supporting energy-demanding immune processes [17–20].

In this model, tissues not critical for immediate survival function primarily as resource donors, whereas phagocytic cells become their priority consumers. This enables maintenance of phagocytosis, reactive oxygen species production, synthesis of inflammatory mediators, and pathogen clearance without requiring a global increase in total energy expenditure [17; 18]. Thus, the systemic aspect of immunometabolic allostasis lies in coordinating resource mobilization with their selective utilization, rather than in isolated catabolism or passive energy conservation.

5.2. Immunometabolic reprogramming of cells

At the cellular level, immunometabolic allostasis is realized through reprogramming of metabolic pathways in phagocytic cells, primarily macrophages and neutrophils [17; 18]. Their functional activity is determined not only by substrate availability but also by local hormonal regulation, which integrates glucocorticoid-mediated control of inflammatory

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intensity with thyroid hormone–dependent tuning of the cellular energy phenotype [5; 11; 19–21].

Within this framework, glucocorticoids limit excessive destructive inflammatory responses while maintaining cellular programs compatible with tissue survival. In contrast, thyroid signaling determines the metabolic efficiency of effector mechanisms, including ROS production, bactericidal activity, and macrophage functional plasticity [21; 23; 32]. Thus, local hormonal regulation represents not an auxiliary but a central element of the immune response. Coordination between systemic and cellular mechanisms ensures that the immune response is not only robust but also metabolically controlled.

5.3. LT_3S as a component of the immunometabolic network

Within the integrative model, LT_3S reflects not an isolated disturbance of thyroid function but a shift in the role of thyroid regulation within the overall structure of the adaptive response [3; 10; 31]. Its clinical significance is determined not solely by the decrease in T_3 levels, but by the context in which it occurs – namely, the intensity of inflammatory stress, its duration, the state of other neuroendocrine axes, and the organism's ability to maintain coordination between systemic and local regulatory mechanisms [10; 22].

In the acute phase, LT_3S may be considered a functionally appropriate component of the immunometabolic network, as restriction of thyroid-dependent energy consumption in peripheral tissues is combined with preservation or reprogramming of local hormone action in immune cells [11; 21]. Under conditions of prolonged or excessive stress, however, this response may lose its adaptive nature and transition into dysregulation. Therefore, LT_3S should be interpreted as an integral indicator of immunometabolic organization rather than merely a marker of disease severity.

5.4. Temporal coordination of the HPA and HPT axes

A key prerequisite for effective immunometabolic allostasis is not only the presence of appropriate hormonal changes but also their temporal coordination. For the HPA axis, this implies preservation of functionally significant rhythmicity of ACTH and cortisol secretion, whereas for the HPT axis it requires alignment of thyroid remodeling with the duration and phase of the inflammatory process [25; 30].

When this temporal coordination is preserved, resource mobilization, redistribution, and cellular utilization occur as interconnected processes. Conversely, loss of glucocorticoid rhythmicity combined with disproportionate or prolonged thyroid remodeling leads to dissociation between central regulation, tissue metabolism, and immune effector function [6; 9; 25; 30]. Thus, the boundary between adaptive remodeling and allostatic overload is determined not only by hormone levels but by the degree of synchronization of their temporal dynamics, receptor sensitivity, and tissue-level implementation.

Summary Statement

Immunometabolic allostasis should be considered a comprehensive model in which the HPA and HPT axes function as interdependent components of a unified cytokine-mediated immunometabolic regulatory complex. This system integrates systemic redistribution of energy resources, cellular metabolic reprogramming, and temporal coordination of the adaptive response.

Within this model, LT_3S acts not as a marker of isolated dysfunction but as a functional element of the immunometabolic network. The effectiveness of this system critically depends on the preservation of integration across its systemic, cellular, and temporal levels. It is precisely the coordination of resource mobilization, redistribution, and utilization that determines the boundary between adaptive remodeling and dysregulation. Disruption of this integration underlies the transition from immunometabolic allostasis to allostatic overload [6; 9; 30; 33].

6. Allostatic overload as a loss of integration between the HPA and HPT axes

The immunometabolic response to systemic inflammation is dynamic and reflects a continuum ranging from coordinated adaptation to a state of dysregulation. During the physiologically controlled phase, interaction between the HPA and HPT axes ensures coordinated mobilization, redistribution, and utilization

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of energy resources. However, under conditions of prolonged or excessive inflammatory burden, the integrity of this regulatory complex progressively deteriorates, leading to allostatic overload as a state of systemic neuroendocrine and immunometabolic dysregulation [1; 2; 15; 30].

A key feature of this transition is not merely a change in the levels of individual hormones, but a loss of their functional coordination. Sustained activation of the HPA axis is accompanied by reprogramming of glucocorticoid signaling, including disruption of circadian and ultradian rhythmicity, as well as the development of tissue-level glucocorticoid resistance [6; 9; 25]. As a result, the hormonal signal loses its capacity to effectively restrain inflammation, thereby contributing to its persistence [5; 20].

In parallel, persistent transformation of thyroid regulation occurs, extending beyond adaptive metabolic switching. Prolonged reduction in T_3 levels, altered T_3/rT_3 ratios, and changes in deiodinase activity are accompanied by impaired tissue-level implementation of thyroid hormone signaling [10; 11; 31]. In this state, the deficit in functional effect is determined not by absolute hormone deficiency, but by reduced efficiency of its cellular action. Consequently, a fundamental dissociation arises between mobilization and utilization of energy resources: glucocorticoid-dependent substrate mobilization is preserved, whereas thyroid-mediated regulation of their utilization becomes ineffective. This leads to metabolic mismatch, characterized by simultaneous catabolism of peripheral tissues and insufficient support of the energetic demands of immune cells [17; 18; 20].

Disruption of integration between the HPA and HPT axes also has significant immunological consequences. Reduced efficiency of glucocorticoid regulation is combined with alterations in the metabolic phenotype of immune cells, contributing to the coexistence of persistent inflammation and immune dysfunction – a hallmark of critical illness [16–18].

Clinically, allostatic overload is manifested by variability and context dependence of therapeutic responses. The effectiveness of glucocorticoid therapy depends not only on dose or timing of administration but also on tissue sensitivity and the integrity of neuroendocrine signal integration [27–29]. At the same time, prolonged reduction of T_3 levels is associated with unfavorable prognosis and reflects loss of adaptive coordination rather than isolated thyroid insufficiency [10; 22].

Thus, allostatic overload should be regarded as a state of loss of integrated regulation between the HPA and HPT axes, in which coordination of temporal, receptor-mediated, and metabolic components of hormonal signaling is disrupted. It is this loss of integration – rather than absolute changes in hormone levels – that determines the transition from adaptation to systemic dysregulation and underlies the development of severe clinical conditions [6; 9; 30; 33].

Operational indicators of loss of integration between HPA and HPT axes may include: a cortisol-to-T3 ratio exceeding 1.5 (nmol/nmol), loss of the normal inverse correlation between morning cortisol and T3 ($r > -0.3$ becomes non-significant), absence of the expected rise in rT3 relative to T3 (rT3/T3 ratio <1.2 despite elevated IL-6), and blunted or absent ultradian cortisol pulsatility (measured by frequent sampling). These criteria are proposed for hypothesis testing in prospective cohorts.

Discussion

The integrative model of immunometabolic allostasis presented in this work proposes a conceptual shift in understanding the neuroendocrine response to critical illness. Within this framework, low triiodothyronine syndrome (LT_3S) is interpreted not as an isolated thyroid dysfunction but as a specific form of thyroid system remodeling occurring during the acute phase of inflammation – particularly during activation of innate (phagocytic) immunity. In this interpretation, the HPA and HPT axes function as a unified cytokine-mediated immunometabolic regulatory complex of the acute inflammatory phase. At the same time, LT_3S represents a component of the broader phenomenon of NTIS, which extends beyond inflammatory conditions and reflects thyroid system adaptation across diverse critical and metabolic states, encompassing both adaptive and dysregulated responses [3; 10; 22].

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The proposed approach expands upon the previously developed concept of context-dependent thyroid adaptation and the immunometabolic role of LT_3S in acute inflammation [12–14], further advancing it by introducing the integration of the HPA and HPT axes as a single regulatory circuit. In this sense, thyroid remodeling is not a byproduct of systemic inflammation but a functionally necessary component of the adaptive response.

Activation of the HPA axis alongside suppression of the HPT axis reflects a coordinated strategy of energy resource redistribution. Glucocorticoids regulate the inflammatory response and mobilize metabolic substrates, whereas reduced T_3 levels limit energy consumption in tissues not essential for immediate survival and promote their catabolic use as energy sources for the immune system [5; 18; 20]. This coordination is consistent with the concept of allostasis [1; 2; 15] and aligns with the model of immunometabolic adaptation proposed in previous studies [12–14].

A key modulating factor in this integration is the temporal organization of hormonal signaling. Disruption of circadian and ultradian rhythms in critical illness leads to reduced tissue sensitivity to hormones and functional dissociation between central and peripheral regulatory mechanisms [25; 30]. Thus, chronobiological disorganization emerges as a critical factor driving the transition from adaptive allostasis to allostatic overload.

Systemic inflammation is also associated with a shift in regulatory mechanisms – from neurotransmitter-mediated control to cytokine-mediated coordination. Proinflammatory cytokines directly modulate both HPA and HPT axis function, altering feedback loops and receptor sensitivity, thereby establishing a regulatory state oriented toward survival [16; 24].

In this context, glucocorticoid resistance should be viewed not only as a loss of anti-inflammatory control but also as a component of tissue-specific remodeling of hormonal sensitivity. Such remodeling may involve preservation of catabolic glucocorticoid effects in donor tissues, while their immunoregulatory effects in effector immune cells are altered. This results in functional dissociation between energy mobilization and its utilization by the immune system, further exacerbating immunometabolic imbalance in critical illness.

Integration of the HPA and HPT axes ensures not only systemic redistribution of energy resources but also direct regulation of innate immune effector mechanisms. Glucocorticoids modulate macrophage and neutrophil function, influencing phagocytosis, ROS production, and pathogen clearance [5; 19; 20], whereas thyroid hormones, through local metabolism – particularly via deiodinase activity – determine the energetic phenotype and functional activity of immune cells [11; 21; 23].

Importantly, key adaptive processes are primarily realized at the tissue level. Local regulation of thyroid hormones within innate immune cells allows maintenance of their functional activity independently of circulating hormone concentrations [11; 21]. This underscores the limitations of approaches focused solely on systemic hormone levels and highlights the importance of tissue-level regulation in immunometabolic adaptation.

The proposed model also helps explain inconsistencies in clinical outcomes. The limited efficacy of thyroid hormone monotherapy across the broader NTIS spectrum – beyond LT_3S – may result from neglecting its interaction with the HPA axis, as well as mismatch between treatment and disease phase or dominant pathophysiological mechanisms [10; 22]. Similarly, the effects of glucocorticoids are context-dependent and determined by the phase of inflammation and individual tissue sensitivity [27–29].

Inflammatory processes are inherently dynamic and phase-dependent. During the acute phase, innate immune mechanisms – including phagocytosis and bactericidal responses – predominate and require substantial energy expenditure [17; 18]. In this context, LT_3S most strongly reflects the early, phagocyte-oriented phase of the immune response, consistent with the concept of thyroid-driven immunometabolic adaptation [12–14], whereas later changes within NTIS may carry different functional implications [3; 10].

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Thus, NTIS should be regarded as a dynamic spectrum, within which LT_3S represents an early adaptive component of immunometabolic remodeling during the phagocytic phase of inflammation. The transition from adaptation to dysregulation is closely associated with loss of integration between endocrine axes [6; 9; 30]. Clinically, this necessitates a comprehensive assessment of neuroendocrine status, including both HPA and HPT axes and their temporal dynamics [25; 30], as well as the development of system-oriented and personalized approaches to hormonal support.

The present model primarily addresses acute systemic inflammation of sterile or infectious origin. However, the interaction between HPA and HPT axes may differ substantially in chronic inflammatory conditions (e.g., rheumatoid arthritis, chronic heart failure) or across etiologies. In viral infections such as COVID-19, the cytokine profile and deiodinase expression patterns show distinct features compared to bacterial sepsis. Chronic inflammation is often associated with persistent low T3 without the same degree of HPA activation. These context-dependent variations should be addressed in future studies, and the current model should be applied cautiously beyond acute settings.

A ***limitation*** of the present work is its conceptual nature, which requires further validation in prospective clinical studies, particularly with regard to chronobiological mechanisms and tissue-level hormonal regulation.

The integrative model of immunometabolic allostasis supports the interpretation of the HPA and HPT axes as a unified cytokine-mediated immunometabolic regulatory complex of the acute inflammatory phase, within which LT_3S emerges not as an isolated endocrine abnormality but as a functional component of systemic adaptation reflecting coordination between immune response and metabolic resources.

Conclusions

Immunometabolic adaptation in the acute phase of inflammation is formed through the function of a unified cytokine-mediated HPA–HPT regulatory complex that integrates systemic and cellular levels of regulation. In this context, LT_3S reflects not an isolated thyroid dysfunction but a component of adaptive immunometabolic remodeling aimed at redistributing energy resources and supporting innate immune effector mechanisms.

Disruption of integration between endocrine axes determines the transition to allostatic overload and systemic dysregulation. Considering LT_3S within the broader NTIS framework highlights the need for integrative, system-oriented approaches to the assessment and correction of neuroendocrine changes in critical illness of both inflammatory and non-inflammatory origin.

Declarations

The authors declare no conflict of interest.

The authors declare that no generative Artificial Intelligence (AI) tools or services were used in conducting the research, preparing, or editing this manuscript for any of the tasks listed in the Generative AI Delegation Taxonomy (GAIDeT, 2025). All stages of the work – from the development of the research concept to the final editing – were performed by the authors.

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Authors' contributions

Contributions / Authors	A	B	C	D	E	F
Biletska O.M.	+	+	+	+	+	+
Horiachyi E.V.				+	+	+
Markovska O.V.			+			+
Latohuz S.I.			+			+
Shevchenko A.S.	+	+		+	+	+

Notes:

A – concept; B – design; C – data collection; D – statistical analysis and data interpretation; E – writing or critical revision of the manuscript; F – approval of the final version for publication and agreement to be accountable for all aspects of the work.

References

1. McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med. 1998;338(3):171-9. DOI: 10.1056/NEJM199801153380307. PMID: 9428819.

2. Sterling P. Allostasis: a model of predictive regulation. Physiol & Behav. 2012;106(1):5-15. DOI: 10.1016/j.physbeh.2011.06.004. PMID: 21684297.

3. Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. Lancet Diabetes Endocrinol. 2015;3(10):816-25. DOI: 10.1016/S2213-8587(15)00225-9. PMID: 26071885.

4. Van den Berghe G. The neuroendocrine response to stress is a dynamic process. Best Pract Res Clin Endocrinol Metab. 2001;15(4):405-19. DOI: 10.1053/beem.2001.0160. PMID: 11800514.

5. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. Nat Rev Immunol. 2017;17(4):233-47. DOI: 10.1038/nri.2017.1. PMID: 28192415.

6. Sobolewska J, Dzialach L, Kuca P, Witek P. Critical illness-related corticosteroid insufficiency (CIRCI): an overview of pathogenesis, clinical presentation and management. Front Endocrinol (Lausanne). 2024;15:1473151. DOI: 10.3389/fendo.2024.1473151. PMID: 39574948.

7. Lazar A. Recent data about the use of corticosteroids in sepsis – review of recent literature. Biomedicines. 2024;12(5):984. DOI: 10.3390/biomedicines12050984. PMID: 38790946.

8. Fredrick FC, Meda AKR, Singh B, Jain R. Critical illness-related corticosteroid insufficiency: latest pathophysiology and management guidelines. Acute Crit Care. 2024;39(3):331-40. DOI: 10.4266/acc.2024.00647. PMID: 39266268.

9. Meduri GU. Glucocorticoid receptor alpha: origins and functions of the master regulator of homeostatic corrections in health and critical illness. Explor Endocrine Metab Dis. 2025;2:101426. DOI: 10.37349/eemd.2025.101426.

10. Langouche L, Jacobs A, Van den Berghe G. Nonthyroidal illness syndrome across the ages. J Endocr Soc. 2019;3(12):2313-25. DOI: 10.1210/js.2019-00325. PMID: 31745528.

11. Boelen A, Kwakkel J, Fliers E. Beyond low plasma T3: local thyroid hormone metabolism during inflammation and infection. Endocr Rev. 2011;32(5):670-93. DOI: 10.1210/er.2011-0007. PMID: 21791567.

12. Biletska OM, Garyachiy YeV, Hurbych OS. Adaptive role of the thyroid system in low triiodothyronine syndrome: immunometabolic mechanisms, clinical significance and rehabilitation perspectives (literature review, part 2). Experimental and Clinical Medicine. 2025;94(4):18p. In press. DOI: 10.35339/ekm.2025.94.4.bgh. [In Ukrainian].

13. Vidart J, Axelrud L, Braun AC, Marschner RA, Wajner SM. Relationship among Low T3 Levels, Type 3 Deiodinase, Oxidative Stress, and Mortality in Sepsis and Septic Shock: Defining Patient Outcomes. Int J Mol Sci. 2023;24(4):3935. DOI: 10.3390/ijms24043935. PMID: 3683534.

14. Biletska OM, Latohuz SI, Garyachiy YeV. Adaptive role of the thyroid system and iodine in low triiodothyronine syndrome: clinical significance and rehabilitation strategies (literature review, part 1). Experimental and Clinical Medicine. 2025;94(3):111-27. DOI: 10.35339/ekm.2025.94.3.blg. [In Ukrainian].

ISSN print 2414-4495, ISSN online 2710-1444, https://msz.knmu.edu.ua, msz.journal@knmu.edu.ua

15. McEwen BS, Wingfield JC. The concept of allostasis in biology and biomedicine. Horm Behav. 2003;43(1):2-15. DOI: 10.1016/s0018-506x(02)00024-7. PMID: 12614627.

16. van der Poll T, Shankar-Hari M, Wiersinga WJ. The immunology of sepsis. Immunity. 2021;54(11):245-58. DOI: 10.1016/j.immuni.2021.01.012. PMID: 34758337.

17. O'Neill LAJ, Kishton RJ, Rathmell J. A guide to immunometabolism for immunologists. Nat Rev Immunol. 2016;16(9):553-65. DOI: 10.1038/nri.2016.70. PMID: 27396447.

18. Buck MD, Sowell RT, Kaech SM, Pearce EL. Metabolic instruction of immunity. Cell. 2017;169(4):570-86. DOI: 10.1016/j.cell.2017.04.004. PMID: 28475890.

19. Barnes PJ. Anti-inflammatory actions of glucocorticoids: molecular mechanisms. Clin Sci (Lond). 1998;94(6):557-72. DOI: 10.1042/cs0940557. PMID: 9854452.

20. Hardy RS, Raza K, Cooper MS. Endogenous glucocorticoids in inflammation: contributions of systemic and local responses. Swiss Med Wkly. 2012;142:w13650. DOI:10.4414/smw.2012.13650. PMID: 22869348.

21. van der Spek AH, Fliers E, Boelen A. Thyroid hormone metabolism in innate immune cells. J Endocrinol. 2017;232(2):R67-81. DOI: 10.1530/JOE-16-0462. PMID: 27852725.

22. Van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. Thyroid. 2014;24(10):1456-65. DOI: 10.1089/thy.2014.0201. PMID: 24845024.

23. van der Spek AH, Bloise FF, Tigchelaar W, Dentice M, Salvatore D, van der Wel NN, et al. The thyroid hormone inactivating enzyme type 3 deiodinase is present in bactericidal granules and the Cytoplasm of human neutrophils. Endocrinology. 2016;157(8):3293-305. DOI: 10.1210/en.2016-1103. PMID: 27355490.

24. Herman JP, McKlveen JM, Ghosal S, Kopp B, Wulsin A, Makinson R, et al. Regulation of the hypothalamic-pituitary-adrenocortical stress response. Compr Physiol. 2016;6(2):603-21. DOI: 10.1002/cphy.c150015. PMID: 27065163.

25. Lightman SL, Birnie MT, Conway-Campbell BL. Dynamics of ACTH and cortisol secretion and implications for disease. Endocr Rev. 2020;41(3):bnaa002. DOI: 10.1210/endrev/bnaa002. PMID: 32060528.

26. Silverman MN, Pearce BD, Biron CA, Miller AH. Immune modulation of the hypothalamic-pituitary-adrenal axis during viral infection. Viral Immunol. 2005;18(1):41-78. DOI: 10.1089/vim.2005.18.41. PMID: 15802953.

27. Annane D, Pastores SM, Rochwerg B, Arlt W, Balk RA, Beishuizen A, et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients. Crit Care Med. 2017;45(12):2078-88. DOI: 10.1097/CCM.0000000000002737. PMID: 28938253.

28. Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, et al. Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med. 2018;378(9):797-808. DOI: 10.1056/NEJMoa1705835. PMID: 29347874.

29. RECOVERY Collaborative Group; Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med. 2021;384(8):693-704. DOI: 10.1056/NEJMoa2021436. PMID: 32678530.

30. Prete A, Yan Q, Al-Tarrah K, Akturk HK, Prokop LJ, Alahdab F, et al. The cortisol stress response induced by surgery: a systematic review and meta-analysis. Clin Endocrinol (Oxf). 2018;89(5):554-67. DOI: 10.1111/cen.13820. PMID: 30047158.

31. Fliers E, Boelen A. An update on non-thyroidal illness syndrome. J Endocrinol Invest. 2021;44(8):1597-607. DOI: 10.1007/s40618-020-01482-4. PMID: 33320308.

32. López-Mateo I, Rodríguez-Muñoz D, de La Rosa JV, Castrillo A, Alemany S, Aranda A. Regulation of metabolic and transcriptional responses by the thyroid hormone in cellular models of murine macrophages. Front Immunol. 2022;13:923727. DOI: 10.3389/fimmu.2022.923727. PMID: 35935955.

33. Chapman KE, Holmes MC, Seckl JR. 11β-hydroxysteroid dehydrogenases: intracellular Gate-Keepers of Tissue glucocorticoid action. Physiol Rev. 2013;93(3):1139-206. DOI:10.1152/physrev.00020.2012. PMID: 23899562.

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ІНТЕГРАЦІЯ ГІПОТАЛАМО-ГІПОФІЗАРНО-НАДНИРНИКОВОЇ ТА ГІПОТАЛАМО-ГІПОФІЗАРНО-ТИРЕОЇДНОЇ ОСЕЙ В ІМУНОМЕТАБОЛІЧНОМУ АЛОСТАЗІ ГОСТРОЇ ФАЗИ ЗАПАЛЕННЯ: ЄДИНИЙ ЦИТОКІН-ОПОСЕРЕДКОВАНИЙ РЕГУЛЯТОРНИЙ КОМПЛЕКС

Актуальність. Гостра фаза запалення супроводжується глибокою перебудовою нейроендокринної регуляції за участю гіпоталамо-гіпофізарно-наднирникової (ГГН) та гіпоталамо-гіпофізарно-тиреоїдної (ГГТ) осей. Підвищення рівня кортизолу та зниження трийодтироніну є взаємопов'язаними компонентами імунометаболічної адаптації, спрямованої на забезпечення енергетичних потреб вродженого імунітету; однак інтеграція системних і тканинних механізмів, що лежать в основі цієї відповіді, залишається недостатньо визначеною.

Мета. Запропонувати інтегративну модель взаємодії гіпоталамо-гіпофізарно-наднирникової та гіпоталамо-гіпофізарно-тиреоїдної осей як єдиного цитокін-опосередкованого імунометаболічного регуляторного комплексу гострої фази запалення, що охоплює системний та клітинний рівні регуляції.

Матеріали та методи. Проведено наративний огляд експериментальних, клінічних та оглядових досліджень (1998–2025 рр.), індексованих у базах PubMed, Scopus, ScienceDirect, EMBASE, MEDLINE, Cochrane Library та Google Scholar. Відбір здійснювали за ключовими словами: синдром низького трийодтироніну, глюкокортикоїди, тиреоїдні гормони, цитокіни, фагоцити, імунометаболізм. Дослідження виконано як приватна ініціатива авторів, без грантової підтримки та державної реєстрації теми.

Етика дослідження. Для аналізу було відібрані лише ті джерела, автори яких чітко дотримувались сучасних біоетичних норм під час проведення їхніх досліджень.

Результати. Під час гострої фази запалення скоординована активація осі ГГН забезпечує мобілізацію енергетичних субстратів, тоді як перебудова осі ГГТ сприяє їхньому функціональному перерозподілу на користь ефекторних механізмів вродженого імунітету. Глюкокортикоїди модулюють інтенсивність та просторову організацію запальної відповіді, тоді як локальна дія тиреоїдних гормонів у фагоцитах, зокрема через дейодиназазалежні механізми, визначає їхній метаболічний фенотип та бактерицидну активність. У цьому контексті синдром низького трийодтироніну (СНТ) постає як компонент адаптивної імунометаболічної перебудови, що має значення для фагоцитарної фази запалення. Порушення координації між осями призводить до алістатичного перевантаження.

Висновки. Імунометаболічна адаптація в гострій фазі запалення формується через функціонування єдиного цитокін-опосередкованого регуляторного комплексу за участю осей ГГН та ГГТ як на системному, так і на клітинному рівнях. СНТ відображає не ізольовану тиреоїдну дисфункцію, а адаптивний перерозподіл ресурсів та регуляцію імунної функції, включаючи бактерицидну активність фагоцитів, що підтверджує необхідність інтегративних підходів до оцінки нейроендокринних змін.

Ключові слова: *ендокринологія, синдром низького трийодтироніну, глюкокортикоїди, тиреоїдні гормони, фагоцити, імунометаболізм.*

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