

Patterns and Mechanisms of Aging: from Molecular to Neurohumoral Disorders

Bon L.I *, Znavets P.A., Malenovskaya M.Y

Candidate of Biological Science, Associative Professor Grodno State Medical University, Belarus.

***Corresponding Author:** Bon L.I, Candidate of Biological Science, Associative Professor Grodno State Medical University, Belarus.

Received Date: 03 August 2026 | **Accepted Date:** 12 August 2026 | **Published Date:** 24 August 2026

Citation: Bon L.I., Znavets P.A., Malenovskaya M.Y, (2026), Patterns and Mechanisms of Aging: from Molecular to Neurohumoral Disorders, *J. Brain and Neurological Disorders*, 9(5): DOI:10.31579/2642-973X/183

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Abstract

The aging process is one of the key objects of study in biology and medicine. In the modern understanding, aging is not a passive involution, but a complex, multilevel and multi-causal destructive process that develops under the influence of exogenous and endogenous factors. Knowledge of the patterns of aging is necessary for an objective assessment of health, prognosis of life expectancy, prevention of age-related diseases (atherosclerosis, hypertension, diabetes mellitus, etc.), as well as for the development of strategies to slow the rate of aging. This section discusses the fundamental concepts of gerontology, the classification of types of aging, modern theories of this process, as well as the molecular, cellular, and neurohumoral mechanisms of age-related changes.

Key Words: biological age; aging; homeoresis; vitaut; etagenesis; heterotopy; adaptive-regulatory theory; DNA repair; microsomal oxidation; antihypoxic system

1.Introduction

1.1. Basic Concepts. Biological Age

For a long time, in idealistic and vulgar materialistic philosophy, life and death were viewed as two categories that negate each other [2, 27].

Knowledge of the patterns of aging development and its mechanisms is necessary for a physician to objectively assess health, predict possible life expectancy, and understand the causes of various diseases [2, 5]. Diseases such as atherosclerosis, arterial hypertension, coronary heart disease and cerebral ischemia, diabetes, and cancer mainly occur in the second half of a person's life and are often associated with the aging process [2, 16]. This is why the most effective means of preventing these diseases are interventions aimed at the rate of aging [5, 27].

A strict distinction should be made between the concepts of aging and old age, cause and effect. Old age is the naturally occurring final period of age-related development [5]. Aging is a destructive process that develops as a result of the increasing damaging effects of exogenous and endogenous factors with age, leading to the insufficiency of the body's biological functions [12, 15]. Aging leads to a limitation of the body's adaptive capabilities, a decrease in its reliability, and the development of age-related pathology [6, 11, 14]. The involvement of environmental factors in the development of aging justifies the search for an optimal lifestyle and ecological conditions that help slow the rate of aging [12, 27]. Environmental factors, acting on biological processes, affect life expectancy [12, 17].

In the course of evolution, along with aging, the process of vitaut also emerged. Vitaut is a process that stabilizes the body's vital functions,

increases its reliability, and is aimed at preventing damage to living systems with age and increasing life expectancy [5, 15]. Thus, age-related development – etagenesis – is the result of the unity and opposition of two processes – aging and vitaut [5, 7]. Their interrelationship determines the features of species-specific and individual life expectancy [16].

The Time of Onset of Old Age. Age periods have no sharp boundaries [3]. With increasing life expectancy, ideas about the time of onset of old age have changed [17]. For example, the average life expectancy in Ancient Rome was 28–30 years, so 40-year-old people were considered old men, and 60-year-olds were considered deponenti (only fit for sacrificing) [16]. According to the WHO classification, ages 45–59 are considered middle-aged, 60–74 are elderly, people aged 75 and older are called old, and those over 90 are called long-livers [11, 14]. The processes of aging and vitaut arise together with the origin of the organism. The change in their relationship divides all individual development into three periods – progressive, stable, and degradational [5, 27].

A distinction should be made between chronological age (the amount of time lived) and biological age [4, 11]. People age at different rates, and their remaining life expectancy and adaptive capabilities at the same age differ significantly from each other [3, 17]. Biological age is a measure of the body's aging, its health, and its remaining life expectancy [3-11]. Determining biological age is very important for distinguishing between physiological and premature aging, developing a system of preventive measures, social organization of a person, conducting pension policy, etc. [3, 4, 13]. The more chronological age exceeds biological age, the slower the rate of aging, and the greater the life expectancy should be [9, 17].

Age-related changes in physiological systems. In humans, age-related changes develop unevenly [5-7]. Often, the rate of aging of some systems, such as the cardiovascular, nervous, and endocrine systems, exceeds the rate of aging of others [18, 19]. This is precisely what creates difficulties in determining biological age, which should comprehensively characterize the aging rate of the entire organism [16-23]. Biological age is determined based on a comprehensive characterization of the functional state of various body systems and an assessment of its adaptive capabilities [9, 13, 14]. This is why, for determining biological age, it is important, on the one hand, to study a set of functions that naturally change with age (visual acuity, hearing, pulse wave velocity, muscle strength, blood pressure, vital lung capacity, etc.), and on the other hand, to extensively use functional tests to establish the level of adaptation of regulatory mechanisms [3, 11].

1.2. Natural and Premature (Accelerated) Aging. Life Expectancy

There are general patterns and fundamental mechanisms of aging in animals of different species and individual specimens [5, 7]. However, along with this, species-specific and individual characteristics of aging are noted [12, 27]. When comparing aging in different animal species, chronobiological changes are distinguished, i.e., those correlating with astronomical time [5]. The greater the species-specific life expectancy, the more pronounced these changes (e.g., age-related changes in connective tissue and vessel walls) [7, 25]. Ontobiological changes correlate with biological age (e.g., changes in the neurohumoral regulation of protein biosynthesis) [19, 27]. Species-specific changes are characteristic of animals of one species and not inherent in animals of another species (e.g., changes in the activity of many enzymes, lipid metabolism) [5, 10]. There are individual aging characteristics specific to individual people [12, 27].

Natural aging is characterized by a certain rate and sequence of age-related changes corresponding to the biological, adaptive, and regulatory capabilities of a given human population [2, 27]. Premature (accelerated) aging is characterized by an earlier development of age-related changes or their greater severity in a particular age period [4, 6]. Premature aging is promoted by past illnesses, adverse environmental factors, including stressful situations, which can affect different links in the chain of age-related changes, accelerating, distorting, or intensifying their normal course [4, 12]. The most frequent manifestations of premature aging in humans are easy fatigability, decreased work capacity, early changes in memory, the emotional sphere, reproductive ability, decreased adaptive capabilities of the cardiovascular and respiratory systems, etc. [4-18]. There is also slowed (retarded) aging, leading to increased life expectancy and longevity [5, 16]. In these cases, age-related changes occur much later than in the population as a whole [17, 20]. A number of population differences in the development of aging are noted [12, 17]. For example, in the USSR, blood pressure levels in older people were lowest among residents of Abkhazia, followed by residents of Ukraine, Moldova, Belarus, and Lithuania [16-18]. Age-related population differences have also been established for some blood parameters – concentrations of cholesterol, phospholipids, lipoproteins, etc. [5, 10].

Species-specific life expectancy varies over a wide range – from a few hours to several decades [5, 27]. A sharp jump in species-specific life expectancy occurred at the human stage [27]. It was associated with the emergence of a high level of adaptive-regulatory mechanisms, the evolution of the brain, thinking, psyche, and the improvement of homeostasis regulation [1, 18, 20]. Over the last 100,000 years, the maximum human life expectancy has increased by approximately 14 years [17, 27]. This increase occurred due to improved habitat, mixing of gene pools of different nations and peoples, and social transformations [12, 17]. An important indicator of public health is the average life expectancy – the number of years a given generation is expected to live on average, provided that the mortality rate of the population in the future remains at the current level [15]. The average life expectancy in our country in 1985–1986 was 69 years (64 years for men, 73 years for

women) [27]. Along with the increase in life expectancy, the difference in this indicator for men and women, associated with a number of social and biological factors, is increasing [17].

One of the most important demographic features of the 20th century is the aging of the population in many countries of the world, i.e., an increase in both the relative and absolute number of people in older age groups [13, 14]. Population aging leads to a change in the structure of morbidity, a greater prevalence of diseases characteristic of the elderly population, the need to study the features of the course and treatment of these diseases, and the development of means to prevent premature aging and improve the working capacity of elderly people [2-16]. Involving pensioners in work and various forms of social activity has a beneficial effect on their health, is a source of moral satisfaction, and maintains vitality for a long time [9, 13].

1.3. General Patterns and Theories of Aging

Aging is associated with changes occurring at all levels of organization of living matter – molecular, subcellular, cellular, systemic, and the level of the whole organism [5, 7, 15]. Regular age-related changes in the body are called homeoresis. Homeoresis is the "trajectory" of changes in the state of physiological systems and the whole organism throughout life [5, 26]. Determining homeoresis allows predicting age-related development, its natural, accelerated, or decelerated aging [4, 12].

The development of aging is characterized by heterochrony – the difference in the time of onset of aging of individual organs and tissues [5, 7]. Atrophy of the thymus, for example, in humans begins at the age of 13–15 years, of the gonads – during the climacteric period (48–52 years in women), while some pituitary functions are maintained at a high level until very old age [19, 27]. Heterotopy – the severity of the aging process – is not the same for different organs and for different structures of the same organ (e.g., aging of the zona fasciculata of the adrenal cortex is less pronounced than that of the zona glomerulosa) [5, 19]. Age-related changes in the body develop at different rates. For example, changes in the musculoskeletal system slowly increase with age; shifts in some brain structures occur late but progress rapidly, disrupting its function [18, 26]. Age-related changes in the body develop in different directions. For example, the secretion of sex steroid hormones decreases, while the secretion of pituitary gonadotropic hormones increases [19].

One of the main patterns of aging of the body is a decrease in its adaptive-regulatory capabilities, i.e., its reliability [2, 11, 14]. These changes are staged. At the first stage – "maximum tension" – due to the mobilization of vitaut processes and the body's adaptive capabilities, the optimal range of changes in metabolism and function is maintained, despite the progression of aging [5, 27]. At the second stage – "decreased reliability" – despite vitaut processes, the body's adaptive capabilities decrease while the level of basal metabolism and function is maintained [2, 11]. Finally, at the third stage, basal metabolism and function change [5, 10]. Consequently, with aging, the ability to adapt to significant loads decreases first, and eventually, the level of metabolism and function even at rest changes [5, 14, 27].

History of the study of aging. Hypotheses and theories. A significant contribution to the formation of modern ideas about the essence of aging was made by the classics of Russian biology – I. I. Mechnikov, I. P. Pavlov, A. A. Bogomolets, A. V. Nagorny [5, 7]. Their research is characterized by a search for fundamental mechanisms of aging and a desire to develop means that affect life expectancy [27]. I. I. Mechnikov put forward the auto-intoxication theory of aging, arguing that aging is the result of autointoxication of the body associated with intestinal function [5]. He believed that by creating a system of rational lifestyle and nutrition, it would be possible to increase human life expectancy [27]. I. P. Pavlov linked the leading mechanisms of aging to changes in nervous activity [18]. Scientists of his school discovered the most important patterns of age-related changes in higher nervous activity [18, 21]. The establishment of Soviet gerontology as an independent problem is

associated with the name of A. A. Bogomolets, who believed that the leading mechanisms of aging are determined by age-related changes in connective tissue [5]. Based on these ideas, he proposed using cytotoxic sera to positively affect the body in old age [27]. A. V. Nagorny and his school collected a large amount of factual material on the features of the aging process and associated this process with the fading self-renewal of protoplasm [5, 15]. One of the synthetic theories of aging is the adaptive-regulatory theory [Frolkis, V. V., 1985] [5, 7].

There are two traditional points of view on the causes of aging development [5, 12].

1. Aging is a genetically programmed process, the result of the natural development of a program embedded in the genetic apparatus. In this case, the action of environmental and internal factors can affect, but to a negligible extent, the rate of aging [12].

2. Aging is the result of the destruction of the body due to the inevitable damaging effect of shifts arising in the course of life itself – a stochastic, probabilistic process [5, 12, 25].

According to the adaptive-regulatory theory, aging is not genetically programmed but is genetically determined by the biological properties of the organism [5, 7]. In other words, aging is a destructive, probabilistic process that develops in an organism with genetically programmed properties [12, 15].

Aging is a multi-causal process caused by many factors, the effects of which are repeated and accumulate throughout life [5, 12]. These include: stress, diseases, activation of free radical oxidation and accumulation of peroxidation products of metabolism, exposure to xenobiotics, changes in hydrogen ion concentration, temperature damage, insufficient excretion of protein breakdown products, hypoxia, and others [5, 10, 25]. Aging is a multi-focal process. It occurs in different cell structures – the nucleus, mitochondria, membranes, etc.; in different cell types – nerve, secretory, immune, liver cells, etc. [5, 7, 15]. The rate of age-related changes is determined by the relationship between aging and vitaut processes [5, 27]. Vitaut mechanisms can be divided into two groups [5, 15].

1. Genotypic – genetically programmed mechanisms [5, 24].

- a) the antioxidant system that binds free radicals [5, 10].
- b) the microsomal oxidation system of the liver, which neutralizes toxic substances [12-17].
- c) the DNA repair system, which eliminates damage to this macromolecule [9, 24].
- d) the antihypoxic system, which prevents the development of deep oxygen oxidation [5, 25].

2. Phenotypic – mechanisms arising throughout life due to self-regulation processes that help preserve the body's adaptive capabilities [5, 27].

- a) the appearance of multinucleated cells [15].
- b) an increase in the size of mitochondria against the background of a decrease in the number of others [25].
- c) hypertrophy and hyperfunction of individual cells under conditions of the death of some of them [15, 26].
- d) an increase in sensitivity to mediators under conditions of weakened nervous control [18, 19].

1.4. Molecular and Cellular Mechanisms of Aging

Disorders of the cell's genetic apparatus. Most researchers associate the primary mechanisms of aging with disorders in the cell's genetic apparatus and the protein biosynthesis program [7, 24]. It has been shown that changes occur at all stages of genetic information transfer – in DNA, chromatin structure, reading (transcription) and transmission (translation)

of genetic information, and protein synthesis [5, 24]. Primary mechanisms of aging are associated with disorders in genome regulation [5, 7]. DNA damage is repaired due to the existence of a special DNA repair system, the activity of which decreases, contributing to an increase in damage to the entire macromolecule and the accumulation of its fragments [8-24]. Significant changes also occur at the stage of translation and assembly of protein molecules [5, 15]. As is known, protein molecules are the basis of life processes. Proteins include enzymes, many hormones, cell receptors, ion membrane channels, and contractile elements of muscle cells [5, 10]. Changes in genome regulation led to uneven shifts in protein synthesis, which ultimately results in cell dysfunction [5, 15]. Enhanced cell activity is ensured by the activation of protein synthesis. In old age, the possible range of stimulation of protein biosynthesis is reduced [5, 27]. According to the error hypothesis, which is widespread but lacks sufficient evidence, errors in genetic information may accumulate with age, leading to the appearance of "defective" proteins [5, 24]. It is assumed that regulatory shifts lead to the activation of genes determining the formation of antibodies to free proteins in the body and to damage to cells and tissues by immune complexes [3, 5].

Disorders of cellular bioenergetics. Significant changes occur at the stage of energy production, transfer, and utilization in the cell [5, 25]. Thus, in many cells, oxygen consumption decreases, the activity of respiratory enzymes decreases, and the content of energy-rich phosphorus compounds – ATP, creatine phosphate – decreases [5, 25]. Activation of glycolysis and increased coupling of oxidation and phosphorylation may have adaptive significance in this case [10, 25]. It is known that the formation of energy potentials occurs in the mitochondria of the cell [5, 25]. With age, the synthesis of mitochondrial proteins decreases, their number decreases, and their degradation occurs, which becomes an important cause of disruption of cellular energetics [5, 25, 27]. Significant changes also occur in lipid metabolism in old age [10]. The phospholipid composition of cell membranes changes, which significantly affects cell function [5, 10]. In the blood, the content of cholesterol, triglycerides, atherogenic lipoproteins, and non-esterified fatty acids increases, while the activity of lipoprotein lipase decreases [2, 10]. All this contributes to the development of atherosclerosis [2, 5].

Decrease in cell mass. Cell dysfunction and their death are the results of aging and affect the activity of organs and the whole organism as a whole [5, 15]. The number of neurons in the brain decreases by 10–20%, and in some brain structures by 30–50%; the number of nephrons in the kidney and alveoli in the lungs decreases by 30–50% [8, 18, 26]. Cell mass in 25-year-old men is 47% of total body mass, while in 70-year-olds it is only 36% [5, 27]. The main morphological manifestation of aging is considered to be atrophy of organs and tissues, characterized by a decrease in the number of parenchymal cells [5, 15]. In each organ, along with atrophying cells, there are normal and hypertrophied cells [15, 26]. The death of some cells leads to a greater load on the remaining cells, which contributes to their hyperfunction and hypertrophy [5, 15].

Cyto-morphological changes. During aging, the nuclear-cytoplasmic relationships in the cell change significantly [5]. An increase in the number of nuclei in the cell, leading to an increase in DNA content, has adaptive significance [5, 15]. A general decrease in the number of mitochondria is often combined with the appearance of giant forms of these organelles [5, 25]. In old age, a pigment – lipofuscin – accumulates in cells, especially non-dividing ones [15, 26]. It is assumed that lipofuscin represents an accumulation of cell waste products and breakdown products of its organelles [5, 15].

Functional changes. Cell functions change significantly: the ability of neurons to perceive information decreases [8, 18]; of secretory cells to synthesize and secrete substances [19]; of contractile heart cells to maintain a high level of performance for a long time [2, 10]. An important manifestation of vitaut is the enhancement of the function of a number of cells during aging, supporting the work of the organ [5, 15]. It is known that at the normal functional level of an organ, not all of its cells and

functional units participate in its activity [5, 27]. This creates a reserve for enhancing function under load. In old age, this reserve is largely already used at rest, which limits the functional capabilities of the organ under load [11-14].

Changes in the cell membrane are of great importance in the mechanism of cell aging [10]. With age, the excitability of many cells decreases, and the duration and shape of the action potential change [5, 26]. Changes in the electrical properties of individual cells are the basis for the development of age-related changes in the ECG, EMG, and EEG [18, 21].

One of the main age-related features of individual cells and cell populations is a decrease in their lability, i.e., the ability to reproduce frequent rhythms of excitation without their transformation [5, 21]. It is known that some cellular formations possess automaticity, i.e., the ability to be spontaneously excited – the centers of automaticity of the medulla oblongata, heart, some blood vessels, intestines, ureters, and others [10]. During aging, the activity of the pacemakers decreases, as does the frequency of their spontaneous depolarization [5, 21]. Calcium ions play a major role in ensuring the coupling between cell excitation and its function [13-19]. During aging, active calcium transport, its uptake and release by cell organelles are weakened, which inevitably impairs cell functions [5, 15].

Sequence and patterns of aging of different cell types. Understanding the sequence of aging of different cell types is of great importance for understanding the aging mechanism of the whole organism [5, 7]. The idea that primary aging is characteristic of non-dividing cells is widespread [15, 26]. Cell division frees the cell from gross age-related changes [5, 15]. A hypothesis has been put forward about the existence of a certain limit of cell divisions, which determines aging and the lifespan of the cell population [15, 24].

In the conditions of a whole organism, cell aging is a complex combination of their own age-related changes and regulatory influences of the entire internal environment of the body [3, 21]. From the perspective of different aging mechanisms, three types of cells are distinguished [4, 15]:

1. Cells characterized by primary aging (nerve cells, connective tissue cells, etc.) [8, 18, 26];
2. Cells whose aging process includes both actual age-related changes and regulatory influences (glandular cells, muscle cells, etc.) [10-19];
3. Cells in which, under natural conditions, aging is mainly secondary and mediated through the entire complex of intraorgan influences (epidermis, epithelium of many organs, etc.) [6, 16].

There are general patterns of aging for all cells and specific aging patterns for cells with different functions [5-7]. Age-related changes in protein biosynthesis, bioenergetics, ion transport, and lipid metabolism are not the same in cells with different functions [7, 10, 24]. Cell function determines the features of its aging [8]. This is why dividing or non-dividing cells with different functions age differently [5-15].

1.5. Neurohumoral Mechanisms of Aging

Age-related changes in neurohumoral regulation are the leading mechanism of aging of the whole organism [1, 18, 19]. They determine changes in thinking, psyche, memory, emotions, work capacity, reproductive ability, homeostasis regulation, and others [18-21]. Primary changes in neurohormonal regulation cause disturbances in the metabolism and function of cells and tissues [5, 19]. Thanks to the mechanisms of neurohumoral regulation, vitaut processes were improved, increasing species-specific life expectancy [5, 27].

Disorders of nervous regulation. Cases are not uncommon where a high level of mental activity persists for decades, until very old age, remaining stable despite significant changes in other organs and systems [18, 27]. The ability to maintain a high level of mental activity for a long time

disproves the notion of aging as involution, i.e., that with aging, phylogenetically younger, more sophisticated mechanisms suffer first, followed by older ones [5, 18].

However, in most cases, in old age, mental rigidity increases – conservatism in judgment, a negative attitude towards the new, praise of the past, a tendency to teach, and overestimation of one's own personality [18, 21]. With age, attention, memory, and psychomotor activity decline; higher nervous activity changes; and due to the disintegration of brain activity, behavioral defects often appear [18, 21]. Retrograde amnesia often develops, characterized by the recall of long-past events and loss of memory for recent events [1-5]. Progressive atherosclerosis is associated with a restructuring of the emotional sphere and a negative coloring of ongoing events [2, 10]. Even I. P. Pavlov's school showed that age-related changes in higher nervous activity are associated with a decrease in the mobility of nervous processes [15-20].

During aging, the functional activity of the brain changes significantly, and the lability of many of its structures decreases [18, 21]. The main electroencephalographic changes come down to a slowing of the alpha rhythm, the appearance or intensification of slow oscillations, and a decrease in the ability to assimilate imposed rhythms [18, 21]. The excitability of individual nerve centers changes unevenly, resulting in a smoothing of differences in excitability in different parts of the brain and the emergence of isoexcitability [5, 12]. This leads to a disruption of the integrative activity of the brain and contributes to the emergence of inadequate reactions and neuroses [18, 21].

In old age, the sensitivity of a number of brain structures to many physiologically active substances increases [13, 19]. Therefore, many centrally acting drugs are prescribed to elderly people in smaller doses [19, 27]. The neurochemical basis of all age-related changes in brain activity is shifts in the metabolism of brain mediators – norepinephrine, dopamine, acetylcholine, serotonin, gamma-aminobutyric acid, etc. [14, 22].

Dysfunctions of the limbic system and the hypothalamus play a significant role in the development of aging and the occurrence of diseases [1, 20, 22]. As is known, the hypothalamus, through neural and hormonal pathways, regulates the state of the internal environment (homeostasis) of the body, metabolism, and organ functions [1, 19]. The connection between age-related changes and hypothalamic activity is so obvious that many researchers "place" the biological clock of the whole body's aging here [1, 20, 22]. During aging, the "reliability" of the hypothalamus as the highest center for regulating all vegetative functions decreases, leading to the development of arterial hypertension, coronary insufficiency, diabetes, i.e., manifestations of a "breakdown" of the central regulation of homeostasis [2, 20, 22]. The role of changes in hypothalamic regulation is especially significant in the development of the climacteric period [1, 19, 20].

The hypothalamic-pituitary region is directly involved in the organization of adaptive reactions during stress (general adaptation syndrome) [1, 19]. In old age, this syndrome is less pronounced, which leads to an increase in the overall damaging effect of stress [5, 12, 19]. Changes in hypothalamic function are associated with shifts in sexual and feeding behavior, as well as in the emotional coloring of behavior [1, 19, 20].

Important mechanisms of aging are associated with the weakening of nervous control over the activity of organs and tissues with age [5, 18]. This leads to metabolic disorders and a limitation of their functional capabilities [5, 10, 18].

Disorders of hormonal regulation. Significant changes occur in hormonal regulation during aging [19]. The concentration of various hormones in the blood changes unevenly in old age – some decrease, others increase, and still others do not change [19, 27]. All endocrine glands are under the control of the hypothalamic-pituitary region [1, 19]. To characterize age-related changes in hormonal regulation, it is necessary to assess shifts in

different links of this complex system [5, 19]. Shifts in the hypothalamus-pituitary-gonads system are of great importance in the aging of the body and the development of the climacteric period [19]. In men, the blood concentration of testosterone progressively decreases, and the content of estradiol and progesterone increases slightly; in women, the content of estradiol and progesterone decreases, while the concentration of testosterone increases [19]. At the same time, the concentration of pituitary gonadotropic hormones – follicle-stimulating hormone (FSH) and luteinizing hormone (LH) – increases with age, which is a compensatory mechanism aimed at maintaining gonadal function [19]. The activity of the hypothalamus-pituitary-thyroid gland system decreases in old age, while the hypothalamus-pituitary-adrenal cortex system remains stable for a long time [19].

In the aging process, insulin deficiency develops [10, 19]. Weakening of the function of pancreatic beta cells, activation of counter-insulin mechanisms, and changes in tissue sensitivity to hormones contribute to the development of diabetes [2, 10, 19].

The central nervous system constantly receives information about the state of the body's internal environment [1, 18]. During aging, significant changes also occur at the feedback stage: reflexes from the heart, blood vessels, and lungs weaken; the reaction of the nerve centers to the action of hormones changes [18-23]. This contributes to a disruption in the regulation of the body's internal environment [1-8].

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DOI:[10.31579/2642-973X/183](https://doi.org/10.31579/2642-973X/183)

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