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ABSTRACT

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MODERN APPROACHES TO NEUROPROTECTION IN TRAUMATIC BRAIN INJURIES, CEREBROVASCULAR DISEASES, AND COGNITIVE IMPAIRMENTS FOLLOWING ANTITUMOR THERAPY

Background. With the increase in life expectancy, the number of patients with neurodegenerative diseases, particularly dementia, is rising. Concurrently, improving survival rates in cancer patients is accompanied by chemotherapy side effects, including cognitive impairments. Approximately 70% of patients after chemotherapy experience memory, attention, and multitasking problems, significantly affecting their quality of life.

Objective of the study was to characterize contemporary approaches to neuroprotection in traumatic brain injuries, cerebrovascular diseases, and cognitive impairments following oncological treatment.

Materials and Methods. Publications were selected from PubMed, Clinical Key Elsevier, Cochrane Library, eBook Business Collection, and Google Scholar, focusing on neuroprotection strategies for traumatic brain injury, cerebrovascular diseases, and cognitive impairments after cancer therapy. The review was prepared following PRISMA guidelines.

Results. Neuroprotection in neurodegenerative and cerebrovascular diseases focuses on reducing oxidative stress, improving mitochondrial function, regulating excitotoxicity, and controlling neuroinflammation. A comprehensive approach that considers the neurovascular unit helps develop new therapeutic strategies for brain protection. Chemotherapy induces cognitive impairments through microglia activation, oxidative stress, and changes in cerebrovascular function. Psychostimulants, antidepressants, and anti-inflammatory drugs may improve cognitive functions, though their effectiveness requires further research. Combined strategies, including physical activity, cognitive-behavioral therapy, and pharmacotherapy, have shown potential for improving cognitive recovery after cancer treatment.

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Conclusions. Neurodegenerative diseases, ischemic stroke, and traumatic brain injury demand new therapeutic strategies. Cognitive impairments following chemotherapy require an integrated approach, combining psychopharmacology, cognitive-behavioral therapy, and physical activity.

Keywords: neuroprotection, traumatic brain injury, cerebrovascular diseases, neuroinflammation, cognitive impairments, cognitive-behavioral therapy.

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СУЧАСНІ ПІДХОДИ ДО НЕЙРОПРОТЕКЦІЇ ПРИ ЧЕРЕПНО-МОЗКОВИХ ТРАВМАХ, ЦЕРЕБРОВАСКУЛЯРНИХ ЗАХВОРЮВАННЯХ ТА КОГНІТИВНИХ ПОРУШЕННЯХ ПІСЛЯ ПРОТИПУХЛИННОЇ ТЕРАПІЇ

Актуальність. Зі збільшенням тривалості життя зростає кількість пацієнтів з нейродегенеративними захворюваннями, зокрема деменцією. Покращення виживаності при ракових захворюваннях супроводжується побічними ефектами хіміотерапії, зокрема когнітивними порушеннями. Приблизно 70% пацієнтів після хіміотерапії мають порушення пам'яті, уваги та багатозадачності, що значно знижує якість життя.

Мета роботи – охарактеризувати сучасні підходи до нейропротекції при черепно-мозкових травмах, цереброваскулярних захворюваннях та когнітивних порушеннях після протипухлинної терапії.

Матеріали та методи. Публікації підібрані з баз даних PubMed, Clinical Key Elsevier, Cochrane Library, eBook Business Collection та Google Scholar за ключовими словами: нейропротекція, черепно-мозкова травма, нейродегенеративні захворювання, хіміотерапія, променева терапія, когнітивні порушення. Огляд підготовлений відповідно до PRISMA.

Результати та обговорення. Нейропротекція при нейродегенеративних і цереброваскулярних захворюваннях спрямована на зменшення окислювального стресу, покращення мітохондріальної функції, регуляцію ексайтотоксичності і нейрозапалення. Врахування нервово-судинної одиниці дає змогу розробляти нові терапевтичні стратегії для захисту мозку. Хіміотерапія спричиняє когнітивні порушення через активацію мікроглії, окислювальний стрес і зміни в цереброваскулярній системі. Психостимулятори, антидепресанти і протизапальні препарати можуть покращити когнітивні функції, проте їх ефективність потребує додаткових досліджень. Комбіновані стратегії, що включають фізичну активність, когнітивно-поведінкову терапію та фармакотерапію, мають потенціал для покращення когнітивного відновлення після лікування раку.

Висновки. Нейродегенеративні захворювання, ішемічний інсульт і черепно-мозкова травма вимагають нових терапевтичних стратегій. Когнітивні порушення після хіміотерапії потребують комплексного підходу, включаючи психофармакологію,

когнітивно-поведінкову терапію та фізичну активність.

Ключові слова: нейропротекція, черепно-мозкова травма, цереброваскулярні захворювання, нейрозапалення, когнітивні порушення, когнітивно-поведінкова терапія.

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INTRODUCTION

In view of the anticipated increase in life expectancy and the growing number of elderly individuals, a significant rise in the population aged between 60 and 80 years is projected by 2030. It is estimated that during this period, individuals over 65 will constitute about one third of the population, while those over 80 will account for approximately one quarter. This demographic aging is leading to a substantial increase in the number of patients suffering from neurodegenerative diseases, particularly dementia, which poses a serious threat to public health. The rising prevalence of these conditions creates significant socio-economic challenges, as they are characterized by a gradual decline in cognitive functions and impose a heavy burden on medical and social systems [1].

On the other hand, remarkable improvements in cancer survival rates have been made possible by scientific advancements in awareness, screening, prevention, diagnosis, and treatment. For example, the average five-year survival rate for breast cancer increased from 75% in the 1975–1977 cohort to 91% in the 2008–2014 cohort. However, this progress also brings new challenges, as most treatment methods – including traditional chemotherapeutic agents and newer approaches – are often accompanied by serious side effects that may be long-lasting or even irreversible. The adverse effects of chemotherapy can significantly deteriorate the overall health of patients, including the development of cognitive impairments with long-term consequences [2].

The impact of chemotherapy on cognitive functions is particularly significant. Chemotherapeutic agents can induce cognitive impairments through several mechanisms, such as damage to the blood–brain barrier (BBB), increased oxidative stress and inflammatory processes in the brain, and disruption of neurogenesis. These factors contribute to impaired neuronal function, which in turn leads to substantial cognitive deficits, including problems with memory, attention, processing speed, and multitasking. Collectively, these issues considerably reduce patients' quality of life, especially during post-treatment rehabilitation. Given the increasing survival rates among oncology patients, these cognitive impairments have become an important concern for healthcare institutions and necessitate the development of new strategies to support these patients [3].

In cancer survivors, chemotherapy can lead to incurable neurological deficits of a chronic nature, commonly referred to as chemotherapy-associated cognitive impairment. Studies indicate that approximately 70% of oncology patients who have overcome the disease report persistent impairments in memory, attention, processing speed, multitasking, and a decline in mental health. These deficits have long-term effects on patients' ability to function normally in everyday life, reducing their capacity for work and social interaction, which in turn affects their psycho-emotional state and overall quality of life [4].

The cognitive consequences of chemotherapy represent a significant issue that requires a comprehensive approach to treatment and rehabilitation, as these impairments can considerably worsen patients' daily functioning, even after recovery from cancer.

The aim of this study was to characterize the current understanding of approaches to neuroprotection in traumatic brain injuries, cerebrovascular diseases, and cognitive impairments following antineoplastic therapy based on data from open-source information.

MATERIALS AND METHODS

Publications were selected from the following databases: PubMed (https://pubmed.ncbi.nlm.nih.gov/), Clinical Key Elsevier (https://www.clinicalkey.com), Cochrane Library (https://www.cochranelibrary.com/), eBook Business Collection (https://www.ebsco.com/), and Google Scholar (https://scholar.google.com/). These sources provided information on neuroprotective approaches in traumatic brain injuries, cerebrovascular diseases, and cognitive impairments following antineoplastic therapy.

In the first stage, a literature search was conducted using the following keywords: neuroprotection, brain, traumatic brain injury, neurodegenerative diseases, cerebrovascular diseases, excitotoxicity,

neuroinflammation, ischemic stroke, cerebral protection, cognitive impairment, chemotherapy, radiotherapy, anti-inflammatory agents, and cognitive-behavioral therapy.

During the second stage, article abstracts were reviewed and publications that did not meet the study criteria were excluded. In the third stage, the full texts of the selected articles were evaluated for compliance with the inclusion criteria and the relevance of the research. The inclusion criteria for publications subjected to content analysis were as follows: 1) coverage of current data on neuroprotective approaches; 2) adherence to the key principles of evidence-based medicine; and 3) open access to the full-text article.

This review was prepared in accordance with the key principles of the PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) guidelines.

RESULTS AND DISCUSSION

1. Neuroprotection in Neurodegenerative and Cerebrovascular Diseases

Neurodegenerative diseases are a group of pathological conditions characterized by the progressive degeneration of neurons in the central or peripheral nervous system. These diseases can develop as a result of damage to various types of neurons or different regions of the nervous system, which in turn determines their clinical manifestations and disease course. Depending on the location of the lesion and the specific pathological changes in neurons, numerous disorders emerge that are accompanied by debilitating symptoms such as cognitive impairments, motor deficits, and emotional disturbances, which can ultimately lead to patient death. Among the most common neurodegenerative diseases are Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. Although these conditions have distinct pathogenetic mechanisms, their overall development indicates common molecular disruptions at the level of neuronal cells.

The process of neuronal degeneration is extremely complex and remains poorly understood. However, at the cellular level, it exhibits a multifactorial nature. This means that multiple pathophysiological processes can occur simultaneously in the organism, contributing to disease progression. Among the most important mechanisms underlying neurodegeneration are oxidative stress, excitotoxicity, mitochondrial dysfunction, and autophagy [5]. Oxidative stress results from the accumulation of reactive oxygen species that damage cellular structures (including lipids, proteins, and DNA), thereby impairing neuronal function. Excitotoxicity, in turn, arises from the excessive activation of glutamate receptors, which leads to a pathological influx of calcium into the cell and ultimately its death [5]. Mitochondrial dysfunction is also a critical factor, as mitochondria provide the cell's energy support; their impairment disrupts cellular metabolism and triggers the activation of programmed cell death. Moreover, autophagy, essential for the normal clearance of damaged organelles and proteins, is found to be disrupted in the process of neurodegeneration, further exacerbating the pathological changes in neurons.

Neuroinflammation also plays an important role in the development of neurodegenerative diseases. Elevated levels of inflammatory cytokines and the activation of microglia can contribute to neuronal damage and even accelerate disease progression. Given the multifaceted nature of these processes, neurodegenerative diseases remain among the most complex and unresolved challenges in modern medicine [6]. To date, there is no effective treatment that can not only halt but even slow the progression of neurodegenerative diseases. This creates a significant burden on patients, their families, and the healthcare system as a whole, since these diseases cause not only severe physical and psychological distress but also enormous economic costs related to treatment and care [7].

Most clinical trials in the field of neurodegeneration have ended in failure, which underscores the need to search for new approaches to treat these conditions. This reflects the complexity of the underlying pathological mechanisms that require novel, more targeted, and comprehensive therapeutic strategies. Nonetheless, despite these challenges, research in this area is actively ongoing, as neurodegenerative diseases (according to the latest estimates) affect over 100 million people worldwide. This highlights the enormous significance of these conditions as a global medical and social problem.

Considering the growing impact of neurodegenerative diseases on public health and the high social and economic costs they incur, an important area of research remains the development of new neuropharmacological agents capable of reducing neuroinflammatory processes, improving brain function, and slowing disease progression [8]. Since there is currently no effective drug for the complete treatment of neurodegeneration, researchers are focusing on developing new therapeutic approaches that can alleviate the severity of symptoms and improve patients' quality of life.

Not less relevant in modern healthcare is the prevention and treatment of cerebrovascular diseases, particularly ischemic stroke. Ischemic stroke develops due to the occlusion of a blood vessel by a thrombus, which disrupts blood flow to or within the brain, resulting in insufficient oxygen and nutrient supply to

brain cells. This leads to their death and significant impairment of brain functions. Ischemic stroke is the third leading cause of death in the Western world and a major cause of disability among adults. This aspect is especially important in the context of an aging population, as the number of individuals suffering from this disease increases each year, thereby creating an enormous burden on healthcare systems and the economy overall. In this regard, developing new effective treatment methods for ischemic stroke that would limit the morbidity and mortality associated with this pathology is of utmost importance [9].

Neurodegenerative diseases and ischemic stroke have distinct developmental mechanisms; however, in both cases, significant neuronal damage occurs, leading to serious impairments in brain function. In neurodegenerative diseases, there is a gradual death of neurons, whereas in ischemic stroke, neuronal cells perish due to disrupted blood supply. Nonetheless, the consequences for patients in both instances can be equally severe: impairments in cognitive functions, motor skills, and emotional stability, which substantially diminish quality of life. Given that current treatment strategies cannot fully restore neuronal function after ischemic stroke or neurodegenerative processes, approaches aimed at reducing or slowing neuronal death remain crucial.

Neuroprotective strategies that are actively being investigated in the context of neurodegenerative diseases can also be successfully applied to the treatment of ischemic stroke. Neuroprotection involves using agents capable of preventing or mitigating neuronal damage resulting from ischemia or neurodegenerative processes. These strategies target molecular mechanisms such as reducing oxidative stress, regulating excitotoxicity, enhancing mitochondrial function, and other processes aimed at preventing neuronal death. Research in this field has shown that neuroprotective strategies can not only slow disease progression but also positively impact brain function after stroke, making them promising for further clinical applications [10].

For decades, researchers in the field of stroke have employed the term “neuroprotection” in a dual context. First, it referred to protecting the entire nervous system (including the brain) during injuries such as ischemic stroke, traumatic brain injury, or cerebral ischemia resulting from cardiac arrest. Second, the term pertained to the rescue of neurons in cell cultures, where ischemia was simulated by inducing oxygen and glucose deprivation or by using glutamate or chemical insults to mimic in vivo processes [10]. However, this paradigm has proven insufficiently effective, likely because the neurovascular unit comprises not only neurons but also other cellular elements that play a vital role in neuroprotection. Therefore, modern approaches to neuroprotection must account for the complexity and interaction of all cellular components, including glial cells and the vascular endothelium, which directly influence the recovery of nervous system function after injury [10].

The primary cause of death and disability among young individuals is traumatic brain injury (TBI), which affects over 50 million people worldwide each year [11, 12]. This condition has serious consequences for patients, as it can cause brain edema, increased intracranial pressure, and an overall deterioration in the patient’s condition. Cell death may begin within minutes or hours after the injury, and the adverse effects can persist for 72 hours or longer [13]. In light of these complications, early diagnosis and prompt medical intervention are particularly crucial, as they can significantly reduce the mortality rate among TBI patients. Intensive care, surgical intervention, and pharmacological treatment contribute to stabilizing the patient’s condition and improving cerebral perfusion, which is critical for preserving brain functionality.

Despite advances in TBI treatment, patients who have experienced a traumatic brain injury often face long-lasting neurological and neuropsychological deficits. These include cognitive, motor, and psychological disorders that significantly deteriorate quality of life. Patients may experience difficulties with concentration, memory, and motor functions, as well as challenges in emotional and mental health, which necessitate prolonged and comprehensive treatment [14]. Therapeutic measures for TBI typically include the surgical removal of hematomas and bone fragments, as well as pharmacological interventions to ensure adequate cerebral perfusion and oxygenation of brain tissue.

Neuroprotection, a strategy aimed at safeguarding neurons from damage, plays a key role in preventing neuronal death in various cerebral disorders, such as neurodegenerative processes, traumatic brain injury (TBI), and ischemic stroke [9, 15, 16]. It is crucial for maintaining central nervous system functions, as it helps minimize neuronal damage and reduce severe consequences for patients. For instance, drugs that inhibit thrombus formation (such as antithrombotic agents or antiplatelet drugs) and thrombolytics that promote the dissolution of existing clots exhibit a certain neuroprotective effect. However, these agents are primarily targeted at the cerebral vascular system and are therefore classified as indirect neuroprotectants [9, 17]. In contrast, drugs that directly affect neurons are classified as direct neuroprotectants because they modulate the biochemical processes occurring within nerve cells following injury.

Following ischemic brain injury, a complex cascade of biochemical processes is initiated that contributes to neuronal death. This process involves several molecular changes, such as the release of glutamate, activation of glutamate receptors, excitotoxicity, and the influx of calcium ions into cells. Moreover, mitochondrial dysfunction and the activation of intracellular enzymes promote the formation of free radicals and the synthesis of nitric oxide, further exacerbating neuronal damage. In addition, processes such as apoptosis (programmed cell death) and inflammation occur, further contributing to the progression of injury [16]. Within this cascade, numerous molecular targets can be pharmacologically modulated, opening up opportunities for developing new neuroprotective strategies capable of limiting or halting neuronal death processes [18]. Thus, effective therapeutic interventions should target these critical molecular pathways to significantly improve treatment outcomes for patients with cerebral injuries.

To date, over 1000 potential neuroprotective agents have been tested in preclinical studies, many of which have shown promising results in protecting neurons and reducing neuronal damage in various cerebral pathologies. These compounds, investigated at various stages of development, include both molecules that directly affect neurons and agents aimed at supporting neuroglia (particularly astrocytes and microglia) which play a vital role in neuroprotection [9]. Many of these compounds have demonstrated encouraging results under laboratory conditions and in animal models, raising hope for potential success in clinical trials. However, it is important to note that the transition from preclinical studies to clinical trials remains challenging and fraught with risks, as many molecules fail to progress through all testing stages due to toxicity or insufficient efficacy in human subjects.

2. The Role of the Neurovascular Unit in the Development of Neuropathologies: Differential Vulnerability

The false assumption that agents found effective in protecting neurons in vitro could be transformed into pharmacotherapeutic strategies for neuroprotection has proven to be erroneous. This is likely due to the fact that the neurovascular unit comprises not only neurons but also other cells that play a crucial role in maintaining normal brain function [10]. The term “neurovascular unit” was proposed to emphasize that the brain is composed of various cell types, each performing specific functions. Within this unit are neurons, astrocytes, endothelial cells, pericytes, and other glial subtypes. Each element plays its role, and active communication among these cells ensures the optimal functioning of brain structures [19].

Meanwhile, the Stroke Therapy Academic Industry Roundtable (STAIR) has proposed a more comprehensive approach to defining the concept of “cerebral protection.” They recommend considering the neurovascular unit as an integrated complex that includes all its components. In this context, studies aimed at protecting neurons have been termed “neuronal protection,” those focusing on astrocytes are classified as “glioprotection,” and investigations directed at the blood–brain barrier have been labeled “vasculoprotection” [20]. This approach allows for a clearer delineation of the roles of different cells in the mechanisms of cerebral protection and promotes a more holistic strategy for developing therapeutic interventions to safeguard the brain from injury.

Cerebral cytoprotection, or simply “cerebral protection,” is a concept that encompasses an approach to treatment aimed at the overall preservation of the brain and its neurological function. This term reflects the modern understanding that effective treatment should not focus solely on individual elements of the nervous system, such as neurons, but on the entire complex of cells that constitute the neurovascular unit. The significance of this concept lies in its recognition of the need to consider the interactions among all cellular components of brain structures, rather than just neurons, as was the case in traditional approaches.

However, one may ask: what is the real benefit of these new definitions if they cannot change the approach to preclinical research and the development of new pharmacological strategies? The answer lies in understanding that new definitions and concepts open up new horizons for research. Thanks to a revised understanding of the neurovascular unit (specifically, how all elements of the brain interact), new avenues of investigation have emerged. This allows for the study not only of individual processes, such as neuronal damage or vascular dysfunction, but also of the interactions among all cellular elements that comprise brain tissue.

Three important ideas that have emerged from this new approach to understanding the neurovascular unit have the potential to significantly alter the direction of scientific research and therapeutic strategies. The first idea concerns an improved understanding of reperfusion injury – a process that occurs when blood flow to the brain is restored after prolonged ischemia. Despite the restoration of circulation, this process can cause additional damage to brain tissue through oxidative stress and other biochemical mechanisms. With a better understanding of these processes, it is now possible to develop new treatment approaches that reduce or prevent such damage.

The second idea involves an enhanced understanding of the neurovascular unit's response to injury. Previously, much of the research was focused on individual components of this unit, such as neurons or blood vessels. However, by considering the entire unit, we can now comprehend how one part of the nervous system interacts with another during trauma or disease, thereby uncovering new possibilities for protecting and restoring the brain after injury.

The third important idea is related to the "help me" signal mechanism within the neurovascular unit. This signal is initiated during brain injury or the disruption of normal function and is part of the recovery processes that activate various cellular responses aimed at restoring homeostasis. A new understanding of this signal allows for better insight into how these mechanisms can be activated at the molecular level, potentially leading to more effective brain recovery following trauma or disease.

These novel approaches and concepts hold tremendous potential for enhancing treatment strategies for numerous neurodegenerative diseases, ischemic stroke, traumatic brain injury, and other cerebral disorders. They not only facilitate the development of more effective treatment methods but also pave the way for new strategies that can significantly alleviate patient conditions and improve functioning in cases of severe neuropathologies [10; 20].

During reperfusion injury, several processes occur that impede microvascular outflow and disrupt the blood–brain barrier. In this phase, damaged mitochondria generate free radicals of oxygen and nitrogen, which mediate cellular damage pathways throughout the neurovascular unit. Endothelial cell injury leads to platelet aggregation and microthrombosis, further exacerbating perfusion deficits [21].

The phenomenon known as selective vulnerability was described about 40 years ago [22, 23]. Neurons were found to be the most vulnerable, followed by astrocytes and then endothelial cells. It was believed that this hierarchy of vulnerability stemmed from the relative distances between cells and differences in microcirculation [24]. Additionally, regional differences in the excitotoxic ratio (the relative density of excitotoxic glutamate versus inhibitory γ-aminobutyric acid (GABA)-ergic synapses) are also linked to selective vulnerability [22]. In contrast to selective vulnerability, which is associated with regional differences in cell death during ischemia, differential vulnerability refers to the inherent susceptibility of the neurovascular unit's components to ischemia in monocultures. In this context, while neurons remain the most vulnerable, astrocytes exhibit the greatest resistance to ischemia; however, the mechanisms underlying differential vulnerability remain unclear [10].

During reperfusion injury, numerous processes with catastrophic consequences for the neurovascular unit occur, including disturbances in microvascular blood flow and the disruption of the blood–brain barrier. A key aspect of this process is mitochondrial damage, as mitochondria begin to actively generate oxygen and nitrogen free radicals during reperfusion. These free radicals are the primary molecules that trigger a cascade of biochemical reactions, mediating further cellular damage throughout the neurovascular unit [21]. They interact with cell membranes, proteins, and DNA, causing oxidative stress that exacerbates tissue damage. Moreover, endothelial cell injury results in platelet aggregation and the formation of microthrombi, which further complicates microcirculation, impairs cerebral blood supply, and leads to even greater perfusion deficits in brain structures.

The process of selective vulnerability of cells, first described about 40 years ago, is an important aspect in understanding why certain cells within the neurovascular unit are more sensitive to ischemic injury than others. During ischemia, neurons are found to be the most vulnerable to damage, likely due to their high metabolic demand and sensitivity to fluctuations in blood supply. Although astrocytes are less vulnerable, they still undergo significant injury. Meanwhile, endothelial cells also suffer damage; however, in most cases, they can restore their function following reperfusion injury. This hierarchy of cellular vulnerability (including neurons, astrocytes, and endothelial cells) results from a complex interplay of metabolic and functional processes, as well as the proximity of cells to blood vessels, which determines their reliance on microcirculation [22, 23].

Selective vulnerability is associated with regional differences in cell damage observed during ischemia. In addition, the concept of differential vulnerability refers to the inherent sensitivity of cells to ischemia as seen in monoculture conditions. Under these conditions, neurons exhibit the greatest vulnerability, while astrocytes display higher resistance to such injuries, suggesting the existence of unique molecular protective mechanisms within astrocytes. However, the mechanisms underlying this differential vulnerability remain insufficiently understood and require further investigation to elucidate how these cells respond to ischemic injury at both molecular and cellular levels (see Fig. 1) [10].

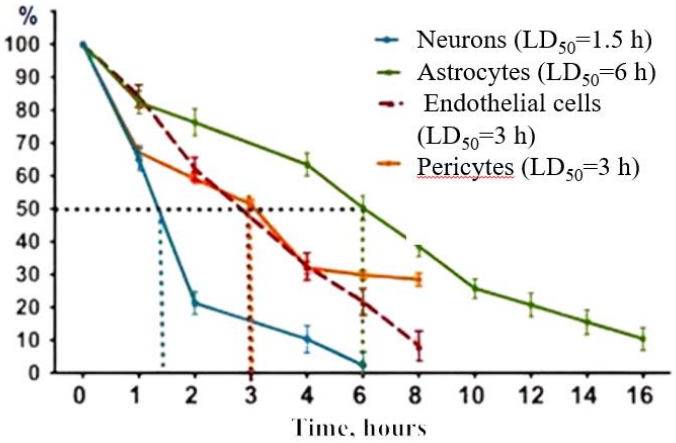

Fig. 1. The effect of oxygen-glucose deprivation on the components of the neurovascular system – brain cell viability (%) during ischemia (adapted from [25])

Studies involving cell cultures exposed to oxygen and glucose deprivation for varying durations have revealed significant differences in the vulnerability of different cell types. Cell viability, assessed 24 hours after ischemic injury, demonstrated that neurons are the most susceptible to ischemic stress, whereas astrocytes show the least vulnerability. Pericytes and endothelial cells exhibit an intermediate level of resistance to ischemia [25]. These findings highlight the importance of understanding the various mechanisms that dictate cellular sensitivity to ischemia and underscore the need to develop therapeutic strategies aimed at bolstering the more resilient cell types.

Furthermore, evidence suggests that during ischemia, neurons activate astrocytes through the release of signaling molecules that indicate a need for assistance. This "help me" signal is a key component of the neuroprotective mechanism, although its precise molecular identity remains under investigation. Currently, thrombin and β2-estradiol are among the candidate molecules believed to play a role in activating astrocytes in response to ischemic injury [26, 27]. Once activated, astrocytes contribute to the protection of neighboring neurons by reducing the extent of ischemia-induced damage. This process confers a degree of neuroprotection that enhances neuronal survival under severe ischemic conditions [25, 28, 29, 30].

3. Mechanisms of Cognitive Impairments Associated with Radiotherapy and Chemotherapy

Despite significant progress in cancer treatment, which has improved patient survival rates, the negative impact of chemotherapy on the central nervous system (CNS) remains a serious issue. In particular, neurotoxicity resulting from therapy and the decline in cognitive functions have been observed in patients for many years. These cognitive impairments include memory loss, disruptions in verbal skills, and a reduced ability to perform complex tasks (executive functions) [31, 32, 33].

Therapeutic methods used in cancer treatment (specifically radiotherapy and chemotherapy) can significantly disrupt neuronal signal transmission in the brain, which in turn leads to persistent cognitive impairments. These deficits may persist even after the completion of the treatment course, thereby diminishing patients' quality of life.

One of the primary mechanisms underlying these changes is the activation of microglia – the immune cells of the CNS that serve as protectors against pathogenic agents. Under the influence of cancer therapy, microglia become activated and initiate a series of alterations in the brain's neuronal networks, including changes in their architecture, thereby disrupting normal neuronal function.

One of the most detrimental consequences of this activation is the suppression of neurogenesis – the process of generating new neurons. This occurs through the inhibition of the proliferation of neuronal precursors and their subsequent differentiation into mature neurons. As a result, the brain's capacity for recovery and adaptation to new conditions is reduced, which can lead to long-term cognitive impairments in patients following cancer treatment [34].

Furthermore, microglia play a crucial role in the maintenance and formation of synapses, which are essential for normal neuronal communication and brain function. They are involved in the pruning of dendrites and axonal terminals, a process that helps sustain synaptic plasticity – the fundamental basis for learning and memory. This mechanism enables the brain to adapt to new information and form new neural connections. However, changes in microglial activation induced by chemotherapy and radiotherapy can lead to aberrant synaptic pruning. This disruption of normal synaptic

transmission may adversely affect cognitive functions. The impairment of this critical microglial role diminishes the brain's ability to properly process information, thereby contributing to the development of cognitive deficits, such as memory problems and decreased concentration levels [34].

Additionally, chemotherapy and radiotherapy can affect the dynamics of myelin – a vital component of nerve fibers critical for the speed and efficiency of nerve impulse transmission between neurons. Myelin sheaths facilitate the rapid conduction of electrical signals, ensuring the effective functioning of neural networks. However, the activation of microglia during cancer therapy may interfere with normal neuronal myelin plasticity, impairing the function of myelin sheaths. This disruption slows down signal transmission in the brain and reduces reaction speed, which can significantly compromise cognitive efficiency. A decrease in nerve impulse conduction speed manifests as increased reaction time and a marked decline in cognitive abilities [34].

The cumulative effect of all these changes in the structure and function of neural circuits in the brain can lead to profound impairments in its functions. This sets the stage for persistent neurological dysregulation manifested by symptoms such as memory impairment, reduced attention span, difficulties in performing complex cognitive tasks, and, in some cases, the development of chronic cognitive disorders. These consequences can significantly deteriorate the quality of life for cancer survivors and, unfortunately, may persist for an extended period after the completion of therapy. In light of these serious outcomes, understanding the mechanisms underlying these changes becomes critically important for developing new approaches to treat cognitive impairments in cancer survivors, particularly through the development of neuroprotective strategies capable of reducing or halting these adverse effects of treatment [34].

Cognitive impairments resulting from chemotherapy, often referred to as "*chemobrain*," represent a major problem for many patients undergoing cancer treatment. This condition significantly affects various aspects of cognitive functioning, including memory, attention, learning capacity, and the ability to perform complex tasks, which can severely interfere with daily life. Consequently, patients may face difficulties in decision-making, reduced work or academic performance, and an overall decline in quality of life. Moreover, cognitive impairments may negatively impact treatment adherence, as patients might experience frustration or despair due to difficulties with concentration or memory [35, 36].

It is estimated that about 30% of patients undergoing chemotherapy experience cognitive impairments, while up to 70% of cancer patients report some degree of cognitive dysfunction during or after treatment [37]. These issues may include problems with short-term memory, concentration, information processing speed, and other cognitive processes. This phenomenon has become the subject of numerous studies aimed at elucidating the mechanisms that lead to cognitive dysfunction in patients.

Evidence that chemotherapy indeed induces cognitive changes comes from multiple sources. For example, numerous studies have employed neuropsychological tests to assess the functioning of various cognitive domains, as well as neuroimaging techniques (such as structural and functional magnetic resonance imaging (MRI) and positron emission tomography (PET)) to investigate changes in brain structures and their activity. Additionally, electrophysiological methods, including electroencephalography (EEG), are used to evaluate brain waves and responses to stimulation, providing further insight into how chemotherapy affects neuronal activity and cognitive functions [38].

Recent animal studies have also confirmed these findings, showing that chemotherapeutic agents can induce structural changes in the brain, particularly in regions responsible for memory and learning. These changes may explain the cognitive impairments observed in patients after treatment. As a result, there is an urgent need for further research to better understand the mechanisms driving these impairments and to develop effective strategies for their treatment or prevention.

Most cytostatic drugs used in cancer therapy can induce oxidative stress in the body's cells, including those of the nervous system. This is an important factor in the development of neurotoxicity observed during chemotherapy. Oxidative stress (both directly through the generation of reactive oxygen species (ROS) and indirectly via impairment of the antioxidant defense system) can lead to neuronal damage and subsequent cognitive dysfunction [31, 38].

In particular, drugs such as cyclophosphamide, doxorubicin, and methotrexate contribute to the development of oxidative stress in the central nervous system. Cyclophosphamide, for instance, leads to increased levels of malondialdehyde and diene conjugates of hydroperoxides, which serve as markers of cellular damage due to oxidative stress in the cerebral cortex [39, 40, 41]. This cellular damage can impair neuronal activity, thereby disrupting memory, attention, and other cognitive functions.

Moreover, it is important to note that chemotherapy may affect cognitive function not only through the direct action of the drugs themselves but also via the hormonal changes they induce. One such effect is the onset of premature menopause in women, which may occur as a result of chemotherapy. The decline in estrogen levels, which is a natural consequence of menopause, is already associated with changes in cognitive functions, particularly a reduction in working memory and other cognitive abilities. This can further impair cognitive performance in women undergoing chemotherapy [38, 42].

Another significant factor is the use of certain medications, such as tamoxifen and aromatase inhibitors for breast cancer or androgen deprivation therapy for prostate cancer, which often lead to decreased levels of hormones, particularly estrogen and testosterone. Since these treatments may be administered alongside chemotherapy or as standalone therapies, their impact on hormonal balance can further contribute to cognitive impairments in patients, especially in the context of hormonal fluctuations [38].

Overall, the neurotoxic effects of chemotherapy are a complex result of both the direct toxic impact of the drugs and the hormonal alterations induced by treatment. This underscores the importance of a comprehensive approach to the treatment and support of patients, taking into account the potential cognitive impairments that may arise during chemotherapy.

Furthermore, genetic variability in genes involved in regulating neural recovery and plasticity can significantly influence individual susceptibility to chemotherapy-induced cognitive changes. Genetic variants that affect neuroplasticity, neuronal recovery, and neurotransmission can largely determine how a patient responds to chemotherapeutic treatment and the extent of cognitive impairments they may experience.

One of these genes is apolipoprotein E (APOE), variants of which – particularly APOE4 – are associated with an increased risk of developing cognitive impairments such as deficits in memory, attention, and information processing speed after chemotherapy. APOE4 is a variant that influences neuroplasticity and the brain's ability to restore neuronal connections, rendering individuals with this allele more vulnerable to the negative effects of treatment [38]. This gene may limit the capacity for the recovery of normal brain functions following chemotherapeutic stress, which could be an important factor in the development of cognitive impairments.

Brain-derived neurotrophic factor (BDNF) is another crucial factor that regulates neurogenesis, synaptic plasticity, and overall neuronal health. The level of BDNF can determine the efficiency of brain recovery after chemotherapy, as this protein supports neuronal viability and promotes the formation of new synaptic connections. Therefore, individual differences in BDNF levels may be reflected in the extent of cognitive recovery after chemotherapy as well as in the brain's resilience to its effects.

Another important gene is catechol-O-methyltransferase (COMT), which is involved in regulating dopamine levels – a neurotransmitter that is essential for cognitive functions such as learning, memory, attention, and motivation. Given that variations in the COMT gene can affect dopamine levels, it is expected that these genetic variants will influence cognitive functions both during and after chemotherapy.

Together, these three genes – APOE, BDNF, and COMT – may help explain the individual differences in the manifestation of cognitive impairments in patients after chemotherapy. They can serve as potential biomarkers for predicting which patients are more likely to develop cognitive deficits and may also assist in developing personalized treatment approaches to minimize these side effects. Studying these genetic variations opens up opportunities for more accurate predictions of chemotherapy outcomes on cognitive functions and for improving the efficacy of cancer treatment.

Inflammation induced by cytostatic agents plays a significant role in the development of chemotherapy-related cognitive impairments. Neuroinflammatory processes, which are major contributors to neurodegeneration, can substantially worsen cognitive functions. Proinflammatory cytokines, such as tumor necrosis factor alpha (TNFα) and various interleukins, are well known for their ability to disrupt memory and other cognitive processes. Although these agents may not directly cross the blood–brain barrier (BBB), cytostatic drugs can stimulate the production of these molecules in the peripheral system. They then enter the central nervous system (CNS), either by crossing a compromised BBB or via receptor-mediated endocytosis.

The entry of proinflammatory cytokines into the brain can trigger gliosis, a marker of CNS inflammation. Activated glial cells initiate further inflammatory responses that lead to neuronal damage and the development of cognitive impairments, such as memory deficits, reduced attention, and impaired learning ability [43]. This underscores the importance of inflammatory processes in the development of chemotherapy-induced cognitive changes. Moreover, these alterations can be exacerbated by the effects of chemotherapy on various cell types that reduce the brain's plasticity.

Another aspect is the cardiotoxic effect of certain chemotherapeutic agents. These drugs can induce changes in the cardiovascular system, leading to impairments in cerebrovascular function. Insufficient blood supply to the brain may compromise its functional activity, resulting in cognitive deficits. Deterioration in memory, attention, information processing speed, and overall cognitive function can be a consequence of such cardiovascular changes [44]. These effects may also interact with other factors, such as increased sensitivity to oxidative stress or alterations in neuronal metabolism, which further exacerbate long-term cognitive impairments. Thus, the negative impact on the cerebrovascular system not only amplifies the neurotoxic effects of chemotherapy but also contributes to chronic cognitive deficits that may persist even after the completion of treatment.

Furthermore, changes in the neuroendocrine system play an important role in chemotherapy-related cognitive alterations. Chemotherapy can affect the regulation of neurotransmitters and hormones, thereby impairing brain functions. One of the factors contributing to these changes is corticosteroids – agents frequently used during chemotherapy to control side effects such as inflammation or edema. Corticosteroids can alter the functioning of the neuroendocrine system, particularly by affecting cortisol levels, which in turn heighten the body's stress responses. This may lead to cognitive impairments such as reduced attention, diminished cognitive agility, impaired analytical and decision-making abilities, as well as the development of depression and anxiety disorders [45].

Chronic elevation of cortisol levels in the blood can have significant consequences for brain health, as this hormone is a key regulator of stress responses, and its prolonged increase can induce structural changes in the brain. For example, high cortisol levels can lead to hippocampal atrophy, which is critical for memory and learning processes. This can complicate the recovery of cognitive functions after chemotherapy, given that the hippocampus plays a vital role in memory formation and spatial orientation.

In summary, the relationship between chemotherapy and cognitive impairments is complex and multifaceted. The impact of chemotherapy on the nervous system is not limited to the direct toxic effects on neurons; it also includes changes in the cerebrovascular system, inflammation, disturbances in neuroendocrine regulation, and cardiotoxic effects, which together can significantly deteriorate cognitive function in patients. Given this, it is important to conduct thorough monitoring and to develop individualized approaches for treating cognitive impairments in patients undergoing chemotherapy [38].

4. Neuroprotective and Psychopharmacological Strategies in the Management of Cognitive Impairments in Oncology Patients

Psychostimulants are among the most extensively studied classes of drugs actively used to correct cognitive impairments in patients following radiotherapy and chemotherapy. Their efficacy and safety have been discussed in numerous studies attempting to determine whether these agents can improve cognitive functions in individuals who have undergone cancer treatment. In particular, many of these investigations have focused on how psychostimulants may alleviate the cognitive difficulties that emerge as side effects of chemotherapy and radiotherapy, although the question of whether they can serve as a primary treatment for these impairments remains insufficiently explored.

It should be noted that existing studies often emphasize cognitive impairments specifically as a side effect of chemotherapy or radiotherapy, and only a limited number of works have examined the possibility of using psychostimulants as a primary method for treating the cognitive problems that occur in such patients. In this context, it is important to mention that although psychostimulants may demonstrate some effectiveness, their results are not always consistently positive and may vary depending on individual patient characteristics and the severity of cognitive deficits [46].

This observation underscores the importance of further research aimed at elucidating the mechanisms of action of psychostimulants in the context of post-chemotherapy cognitive dysfunction, as well as the need to develop more specific therapeutic approaches tailored to the needs of different patient groups. Studies should also account for potential side effects, since the use of psychostimulants in treating cognitive impairments may carry various risks, including dependency and serious cardiovascular complications.

For example, modafinil and methylphenidate – both are psychostimulants – have demonstrated some improvements in cognitive functions in several studies. These drugs may be beneficial for enhancing attention, improving memory, and increasing concentration in patients who have undergone chemotherapy or radiotherapy. They have the potential to significantly alleviate the cognitive difficulties characteristic of the so-called "chemobrain"; however, the results are not always consistent. Some studies have reported moderate or mild improvements in cognitive functions following the administration of modafinil and methylphenidate [47, 48, 49], while others have failed to confirm such effects or found only minimal changes in the cognitive status of patients using these agents [50, 51, 52].

Such contradictory findings may be due to various factors, including methodological differences among

studies, variations in dosing and treatment duration, as well as individual patient characteristics. For instance, differences in the doses of modafinil and methylphenidate used may have influenced their efficacy. Moreover, disparate methods for measuring cognitive functions can yield different outcomes, complicating comparisons of psychostimulant effectiveness. Individual factors such as age, comorbid conditions, and the severity of cognitive impairments may also significantly affect treatment response.

These issues highlight the need for further research to better understand the specific mechanisms by which psychostimulants improve cognitive functions. Additionally, it is necessary to determine whether strategies can be developed to enhance the efficacy of these drugs for treating cognitive impairments in patients who have undergone chemotherapy or radiotherapy. A systematic investigation into optimal dosing, treatment duration, and careful consideration of individual patient characteristics is essential for achieving better outcomes and formulating more precise clinical recommendations for the use of psychostimulants in this population.

Thus, although psychostimulants (particularly modafinil and methylphenidate) have shown potential in treating cognitive impairments in cancer patients, their efficacy remains a subject of scientific debate. They have demonstrated the ability to improve attention, memory, and concentration in some patients; however, the results of studies are inconsistent and further research is needed to determine the most effective approaches and optimal dosing regimens [46]. This underscores the need for a deeper understanding of the mechanisms of action of psychostimulants and their impact on the cognitive functions of patients who have undergone cancer treatment, particularly chemotherapy and radiotherapy.

Regarding donepezil, a drug commonly used to treat dementia, early studies on chemotherapy- or radiotherapy-induced cognitive impairments have also shown some promise. Research indicates that donepezil may improve cognitive functions (particularly attention, memory, and learning capacity) in some patients who have undergone cancer treatment [53, 54]. However, the effects of donepezil appear to be limited and may vary considerably based on individual patient characteristics such as age, overall health, and specifics of the cancer treatment regimen. This suggests that donepezil is not a universal solution for treating cognitive impairments in all cancer survivors and underscores the need for an individualized approach in its application.

Memantine, another drug that is sometimes used for the treatment of cognitive impairments, has shown ambiguous results in studies. In some works, memantine demonstrated some improvement in cognitive functions in patients who have undergone chemotherapy or radiotherapy; however, other studies failed to confirm significant changes in the cognitive status of these patients [55]. This variability in results also indicates the need for further scientific research aimed at gaining a deeper understanding of the mechanisms of action of memantine and its potential application in treating cognitive impairments in cancer survivors. At the same time, it is worth noting that memantine, like donepezil, may be more effective in certain cases but is not a panacea for all patients who have undergone cancer treatment.

Thus, despite some positive results in studies regarding the use of psychostimulants, donepezil, and memantine for treating cognitive impairments in patients following chemotherapy or radiotherapy, the question of their efficacy remains unresolved. Further research is necessary to clearly determine which drugs can provide a lasting improvement in cognitive functions, as well as to clarify the individual factors that affect treatment outcomes.

In general, although these drugs (particularly psychostimulants, donepezil, and memantine) demonstrate some potential, their effectiveness in treating cognitive impairments after chemotherapy or radiotherapy remains a subject of scientific debate. This highlights the need for additional clinical studies aimed at more precisely determining the optimal conditions for their use, including dosing, treatment duration, and the individual aspects that may influence therapeutic outcomes.

As noted above, one of the possible causes of chemotherapy-induced cognitive impairments is an imbalance between pro- and anti-inflammatory cytokines. Cytokines, as mediators of inflammatory processes, play an important role in the development of depressive states and cognitive disorders induced by chemotherapy. A shift in this balance can lead to enhanced inflammatory responses, which in turn contribute to the development of neuropsychiatric symptoms such as depression and memory impairments. In view of this, cytokines may become interesting targets for therapeutic interventions aimed at reducing the symptoms of both depression and cognitive impairments in patients after chemotherapy. This approach opens up prospects for the use of antidepressants in the treatment of chemotherapy-related cognitive disorders.

In addition to their traditional impact on monoaminergic systems, antidepressants may also exert effects on neuroplasticity, neuroinflammation, and neurotoxicity. It has been shown that they can suppress progressive neuroinflammation, reduce the neurotoxic impact on brain tissue, and promote the improvement of long-term neurogenesis. These effects are important for the restoration of cognitive functions, especially after

aggressive oncological treatments. At the same time, there is evidence that anti-inflammatory drugs may act synergistically with antidepressants, enhancing their therapeutic effectiveness. This allows for the development of combined therapeutic approaches that could be more effective in treating cognitive impairments associated with chemotherapy.

In order to fully realize the potential of antidepressants for treating chemotherapy-induced cognitive disorders, additional research is necessary to explore their yet-unstudied mechanisms. It is especially important to investigate their effectiveness in the context of the multifactorial causes and symptoms of cognitive impairments. Such studies may allow for a better understanding of how antidepressants and anti-inflammatory drugs interact and whether they can become key components of therapy to improve the cognitive health of patients after oncological treatment [56].

Boullon L. et al. (2021) [57] propose the endogenous cannabinoid system as a new therapeutic target for treating chemotherapy-induced cognitive impairments. The neuroprotective role of the endogenous cannabinoid system, well documented in the context of other neuropathological disorders associated with cognitive dysfunction, holds significant potential for reducing the activation of pro-inflammatory cytokines. These cytokines are actively involved in the neuroinflammatory processes occurring in the brain and are key mechanisms underlying the development of chemotherapy-induced cognitive impairments. Numerous studies confirm that the endogenous cannabinoid system is capable of lowering the level of inflammatory processes that are major contributors to neurodegenerative changes in the CNS.

It is known that cannabinoid drugs can reduce the negative effects of oxidative stress and promote the restoration of neuroplasticity, which, in turn, may aid in the treatment of chemotherapy-induced cognitive impairments. Investigating previously unknown endocannabinoid components that may be important for the molecular modulation of cognitive functions is an important step toward developing new therapeutic strategies [57].

In addition to pharmacological interventions, the most established efficacy is observed in approaches to cognitive rehabilitation, particularly cognitive-behavioral therapy (CBT). Recent reviews indicate that CBT and brain training are among the most promising approaches for improving cognitive functions in cancer survivors [46, 58, 59]. They have demonstrated significant effectiveness compared to other interventions, such as pharmacotherapy or traditional rehabilitation methods. Specifically, CBT not only promotes the improvement of cognitive functions but also helps patients cope with the emotional and psychological consequences of cancer treatment. This approach has the potential to enhance quality of life and reduce levels of anxiety and depression, which often accompany cognitive impairments. Moreover, brain training, which typically includes exercises designed to improve memory, attention, and other cognitive functions, has proven to be an effective means of restoring the cognitive abilities of patients who have undergone oncological treatment [60].

Equally important is the role of physical exercise in improving cognitive functions. It has been shown to be extremely beneficial for both patients with oncological diseases and the general population. According to research, regular physical activity can significantly enhance memory, attention, and learning capacity, reduce stress and depression levels, and contribute to overall improvements in mental health. Furthermore, physical exercise has been demonstrated to reduce the risk of developing cognitive impairments in the future.

One of the primary mechanisms by which physical activity improves cognitive functions is the stimulation of neuroplasticity – the brain's ability to change its structure and function in response to experience. Regular physical exercise activates processes that promote the formation of new neurons and the strengthening of connections between them, directly enhancing memory, attention, and learning capacity. This is particularly important for patients who have undergone chemotherapy or radiotherapy, as these treatments can lead to reduced neuroplasticity and the development of cognitive impairments.

Thus, to achieve the best possible outcomes in restoring cognitive functions in patients after cancer treatment, it is important to combine pharmacological interventions with methods such as cognitive-behavioral therapy, brain training, and physical activity. All these approaches hold significant potential; however, for their successful application it is necessary to gain a deeper understanding of the mechanisms through which they affect the brain, as well as to consider the individual needs and capabilities of the patients.

Another important mechanism by which physical activity influences cognitive functions is the release of cytokines, which play a key role in regulating inflammatory processes in the body. Cytokines are molecules that govern inflammatory responses, and their balance has a direct impact on brain health. Physical exercise helps maintain the balance between pro- and anti-inflammatory cytokines, which, in turn, can reduce neuroinflammation – a critical factor in the development of cognitive impairments following chemotherapy or radiotherapy. Restoring normal inflammatory processes in the brain is essential for improving cognitive functions,

as chronic neuroinflammation can lead to neuronal damage and a decline in their functionality.

At the same time, physical exercise promotes better mitochondrial health – the energy powerhouses of cells that provide the necessary energy for proper neuronal function. Enhancing mitochondrial efficiency helps sustain cognitive functions, since neurons require a substantial amount of energy to perform tasks such as signal transmission, information storage, and stimulus processing. A decline in mitochondrial function can disrupt neuronal activity, whereas physical exercise contributes to the restoration of this function, thereby positively affecting cognitive abilities.

Moreover, physical exercise improves brain metabolism, which includes enhanced blood circulation and the transport of oxygen and nutrients to neurons. This, in turn, helps preserve cognitive functions by ensuring that the brain receives the resources it needs for effective performance. Increased cerebral blood flow also helps reduce the levels of stress hormones such as cortisol, and it stimulates the release of neurotrophic factors that promote the growth of new neurons and the strengthening of synaptic connections.

Another important aspect to consider is the regulation of the gut microbiota. Recent studies have shown that physical activity can positively affect the composition of the intestinal microbiota, which, in turn, may have beneficial effects on brain health. The interaction between the gut microbiome and brain function is becoming increasingly clear, and scientists are beginning to understand how changes in the microbiota can influence cognitive functions and mental health. Regular physical exercise can improve the state of the microbiota, leading to a reduction in inflammatory processes in both the body and the brain, as well as enhancing overall mental health.

Together, these mechanisms create a powerful foundation for supporting and improving cognitive functions in patients who have undergone cancer treatment. They not only help preserve or restore cognitive abilities but also have the potential to reduce the risk of developing long-term cognitive impairments, such as Alzheimer's disease or other neurodegenerative disorders. Physical activity, when combined with cognitive-behavioral therapy and brain training, can become a key component of comprehensive treatment for cancer survivors. Such an integrated approach significantly improves patients' quality of life by reducing the risk of cognitive problems associated with oncological treatment and helping to prevent their development in the future [60, 61, 62].

PROSPECTS FOR FUTURE RESEARCH

Future research is focused on deepening our understanding of the molecular mechanisms underlying neurodegeneration and chemotherapy-induced cognitive impairments, as well as on developing individualized therapeutic approaches that take into account patients' genetic variations. In addition, an important direction involves the investigation of new neuroprotective agents and combined therapeutic strategies that integrate pharmacotherapy, cognitive-behavioral therapy, and physical activity, along with studies examining the impact of neuroendocrine changes and the long-term effects of treatment. All these research endeavors will contribute to the development of more effective methods for the treatment and prevention of cognitive impairments in patients following oncological treatment.

CONCLUSIONS

1. Neurodegenerative diseases, ischemic stroke, and traumatic brain injury are serious medical issues that significantly affect patient health and healthcare economics. Existing therapies are insufficient to halt neuronal death; however, the development of neuroprotective strategies opens new opportunities for improving the treatment and prevention of these disorders, thereby enhancing patients' quality of life and reducing societal costs.
2. Understanding the role of the neurovascular unit in the development of neuropathologies is changing the approach to treating brain disorders. Defining terms such as neuronal protection, glioprotection, and vasculoprotection enables the creation of more effective therapeutic strategies for preserving brain function and preventing damage, opening new prospects for the treatment of ischemic stroke and neurodegenerative diseases.
3. Cognitive impairments following chemotherapy and radiotherapy are a serious problem for cancer survivors. The mechanisms underlying these impairments include microglial activation, oxidative stress, hormonal changes, and genetic variations, which lead to deficits in memory and attention. The prolonged impact of these effects on quality of life underscores the need for new strategies for the prevention and treatment of cognitive impairments with an individualized approach to patients.
4. Cognitive impairments in cancer survivors require a comprehensive approach to correction. Psychopharmacological methods, such as psychostimulants, donepezil, and memantine, show potential, but their efficacy requires further investigation. Cognitive-behavioral therapy, brain training, and physical activity also play important roles. The individualization of treatment approaches and further scientific research are essential for achieving the best outcomes in the management of cognitive impairments.

AUTHOR CONTRIBUTIONS

Hladkykh F.V. – Conceptualization, study design, writing of the main text, and formulation of conclusions.
Liadova T.I. – Participation in the discussion of the obtained results and editing of the article text.
Matvieienko M.S. – Participation in the discussion of the obtained results and editing of the article text.
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