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Astrocytes and their Phenomenal Possibilities in the Treatment of Various Neurodegenerative Disorders: An Overview

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Authors' contributions

This work was carried out in collaboration among all authors. Author AYM designed the study and wrote the first draft of the manuscript. Authors KLB and ZAA managed the analyses of the study. Authors SOK, KAZ and TAG managed the literature searches. Authors ENS and MAA has been involved in writing of the article. Authors AEM and SNP organized needed resources and carried out writing and editing. All authors read and approved the final manuscript.

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ABSTRACT

At present, research in the field of the brain does not cease to surprise us with new facts and discoveries that no one could have suspected about 30 years ago. But it was at the time when it became clear that the cerebral neurons are not the only cells that can respond to changes in the

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external environment. A real scientific boom began to study a heterogeneous group called glia. And scientists are paying close attention to the largest of them – astrocytes. Understanding the importance of astrocytes in the mechanisms of repair and damage to brain cells in various forms of CNS pathology determines the possibility of targeted search for drugs that affect the rate of development of reactive astrogliosis in response to various brain injuries. At the same time, pharmacological modulation of activated astrocytes and other components of glia can be an integral part of the therapy of neurological diseases.

Keywords: Astrocytes; astroglia; neuroinflammation; Alzheimer's disease; astrocyte transplantation; neurodegenerative disorders; melatonin.

1. INTRODUCTION

What are astrocytes and why do we know so little about them?

Since school, we are familiar with the concept of "glia", but even medical students pay a minimum attention to it, assigning only a secondary role of supporting, trophic, protective cells and no more. Today, we can safely say that there are at least two large and very complex networks in the brain: neural and astrocytic, and the latter accounts for 50 to 75% of the total volume of the brain [1].

It is known that in different parts of the brain, the ratio between neurons and astrocytes varies significantly. For example, in the gray matter cortex, it is 1.65 astrocytes per neuron, and in the thalamus, this ratio is already 17:1. Histological studies indicate that in different areas of the brain, astrocytes are not only heterogeneous, but also astrocyte-related complexes in the form of glial synthetium, which can form non-overlapping cell islands. Each astrocyte has its own precise localization, and none of the most numerous processes enters the territory of another astrocyte [2].

Astrocytic cells are connected to each other not by synapses, like well-known neurons, but by specific GABA contacts, in which there are hemi-channels. Simply put, such contacts are also called gap-shaped contacts (gap junction). Recent studies have shown that in the course of evolutionary development, astrocytic cells tend to acquire more processes, and the number of types of astrocytes has increased [3].

It is proven that unlike small rodents, which have only two groups of astrocytes (fibrous cells mainly in white matter and protoplasmic cells – in gray), humans have at least five established types of astroglia. Some have short processes, while others have long "smart" processes that penetrate into different parts of the central nervous system. The functional significance of integrative processes still needs to be studied. The appendages have vesicular extensions at the ends that contact the soft meninges, thus enabling astroglia to participate in the regulation of regional blood flow, energy, ion, and water metabolism, immune defense, and even neurogenesis [4]. These "legs" play a role in limiting the free diffusion of various substances in the central nervous system. With their help, astrocytes can absorb potassium ions and neurotransmitters, metabolizing them and thus create a kind of buffer that blocks direct access for these substances to the extracellular environment around neurons, thereby regulating the composition of the microenvironment. This also allows astrocytes to occupy an intermediate position between the vascular network and neurons and participate in glucose transport due to the large number of glucose carriers [5,6].

One of the most important questions is the mechanisms of astrocyte-neuronal interactions. There is already a clear idea of the existence of the so-called tripartite synapses, where the astroglial process is included in the synaptic space between two neurons [7]. This allows the neuroglia to contribute to the processes of neuronal transmission, and, as it turned out, to the neurons - to the functions of astrocytes (Fig. 1).

(A) Functions of the astrocytes in physiological conditions, which are in favor of the homeostasis of the nervous tissue.
(B) Reactive astrocytosis, which has a double function highly discussed, one for cell death and one for pro-neuroprotection probably in a context dependent-mode.
(C) Astrocytes with genetic modifications by reduced expression of some upregulated genes, which would allow preserve them as a neuroprotective source for promoting neuronal survival; although the mechanism of how they

could maintain this state of neuroprotection for longer time is still.

Recent data have revealed many active roles for these cells both in maintenance of the normal physiological homeostasis in the brain as well as in neurodegeneration and disease. Moreover, human astrocytes have been found to be much more complex than their rodent counterparts, and to date, astrocytes are known to actively participate in a multitude of processes such as neurotransmitter uptake and recycling, gliotransmitter release, neuroenergetics, inflammation, modulation of synaptic activity, ionic balance, maintenance of the blood-brain barrier, and many other crucial functions of the brain [8].

Current evidence strongly supports the notion that non-cell autonomous mechanisms contribute to the demise of neurons in neurodegenerative disorders, and glia causally participate in the pathogenesis and progression of these diseases. In addition to microglia, astrocytes have emerged as key players in neurodegenerative diseases and will be the focus of the present review. Under the influence of pathological stimuli present in the microenvironment of the diseased CNS, astrocytes undergo morphological, transcriptional, and functional changes and become reactive. Reactive astrocytes are heterogeneous and exhibit neurotoxic (A1) or neuroprotective (A2) phenotypes. In recent years, single-cell or single-nucleus transcriptome analyses unraveled new, disease-specific phenotypes beyond A1/A2. These investigations highlighted the complexity of the astrocytic responses to CNS pathology. The present review will discuss the contribution of astrocytes to neurodegenerative diseases with particular emphasis on Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and frontotemporal dementia. Some of the commonalties and differences in astrocyte-mediated mechanisms that possibly drive the pathogenesis or progression of the diseases will be summarized. The emerging view is that astrocytes are potential new targets for therapeutic interventions. A comprehensive understanding of astrocyte heterogeneity and disease-specific phenotypic complexity could facilitate the design of novel strategies to treat neurodegenerative disorders [9].

The last 13 years of research have shown that astrocytes have a signaling function and are involved in the release of so-called glia transmitters (similar to neurons – neurotransmitters). Moreover, the mechanism of release can be both vesicular and membrane (i.e., the release of substances through the pores of the membranes). This is a calcium-dynamic process, since with an increase in calcium in astrocytes, GABA, glycine, glutamate and a

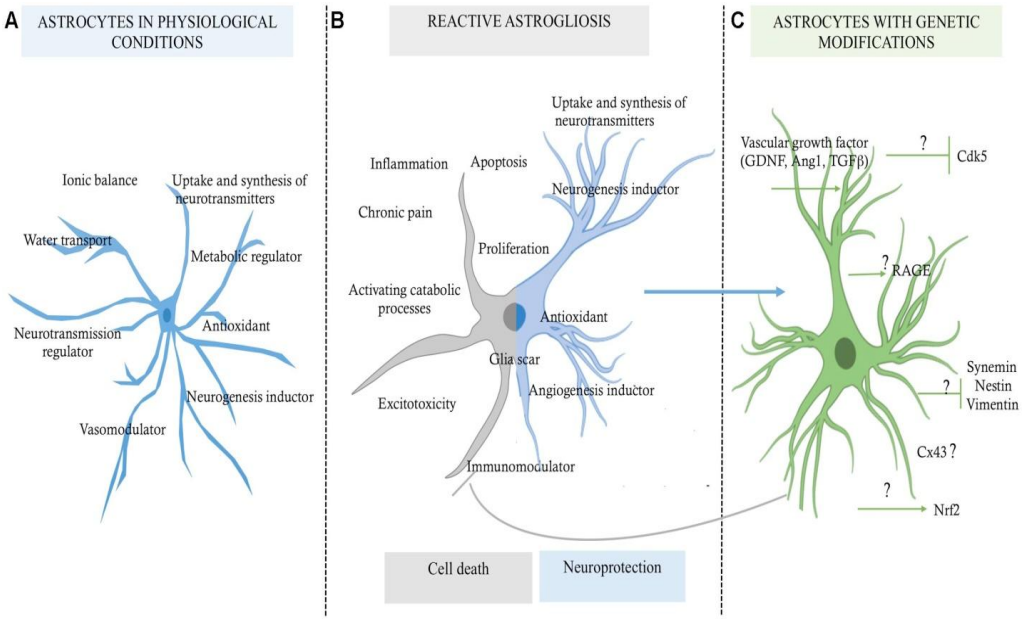

Fig. 1. Function of the astrocytes

mass of other neurotransmitters are released. Glia transmitters activate specific receptors both on the astrocytes themselves and on the neurons themselves (Synaptic NMDAR (GluN2A) and Extrasynaptic NMDAR (GluN2B) [10-14]. From this we can conclude that astrocytes affect a huge number of functional parameters of neurons, including synaptic plasticity, which is impossible without the activation of the astrocyte coagonist-D-serine. Something to be noted is that synaptic plasticity is the basis of learning and memory. It is assumed that without the"resolution" of astrocytes, this basis is impossible. In support of the latter, we can cite an example of an interesting experiment by foreign scientists with progenitor cells of human astrocytes, which were injected into the brain of mice, after which they became smarter. They performed better on logic and memory tests than the control group mice [15-18].

An important discovery is that the aging of the brain undergoes a cognitive decline associated with a decrease in the number of functional capabilities of neuronal synapses in conjunction with changes in the metabolism in the astroglia. Quite recently, by creating transcriptomes of an elderly and young astrocyte in different areas of the mouse brain, scientists sequenced the genes of these astrocytes, which made it possible to identify regional changes in aging. Mutations were found in the genes of aging astrocytes, which affected the changes in the homeostatic and neurotransmission functions of the cells. Although these changes are minimal, aging astrocytes resemble reactive ones in their structure and express genes responsible for synaptic elimination and neuronal damage. This potentially contributes to a decrease in cognitive ability and memory (which is observed in aging) [19-21].

In turn, it has recently been proven that neurons alter the expression of astrocytic metabolic enzymes by secreting a hitherto unknown molecule into the extracellular space. Experimental evidence is presented that the substance transeterine (TTR) isolated from neurons stimulates the expression of glycolytic enzymes in astrocytes, which is reflected in an increase in the synthesis of ATP. However, the action of TTP is differentiated by two regulatory glycolysis enzymes: phosphofructokinase P (PFKP) and pyruvate kinase (PKM1/2 isoforms), which indicates the participation of TTP in the mechanisms in which neurons stimulate the degradation of glycosine units derived from glycogen by astrocytes [22-24].

Another proof of the effect of neurons on astrocytes was the experimental induction of mitochondrial DNA depletion in mouse neurons by inactivating mtDNA replicative heterase (TwKO). The results were stunningly visual. Astrocytic cells are pathologically activated by mtDNA deficiency, which leads to early spontaneous degeneration of the brain tissue parenchyma and astrogliosis. Thus, scientists came to the following conclusions: astrocytes depend on the integrity of mtDNA; mitochondrial metabolism contributes to their activation; pathological activation of astroglia has permissive consequences and that astrocytes are a potential target for interventions in the treatment of various neurodegenerative disorders [25-28].

To understand the functional features of astrocytes, it is necessary to once again look at their morphology. In the cytosol of cells, there are intermediate filaments that perform supporting functions in the central nervous system. They also contain an important peptide marker of astrocytic activity-glial fibrillar acid protein (GFAP), which plays an important role in the processes of regeneration, synaptic plasticity and reactive gliosis. However, in some areas of the brain, including the thalamus (where, paradoxically, the concentration of astrocytes is highest), the expression of GFAP in astrocytes is low. To study the function of astrocytes in the thalamus, which serves as a relay station, there is a great need to identify an alternative-specific marker for astrocytes in the thalamus. A new astrocyte-specific marker, ALDH1L1, has recently been identified. With the help of gene therapy associated with the adeno-associated virus (AVV), it was proved that the ALDH1L1 marker does indeed show the specificity of astrocytes in the thalamus (it may even be useful for targeting in gene therapy against various brain diseases) and its expression increases during gliosis [29].

The close connection of astrocytes with almost any structural element of the brain and their morphofunctional feature makes them one of the first targets to take on the effects of adverse factors, actively involving them in the genesis and limitation of various brain lesions, not only organic, but also functional. In turn, this leads to the above-mentioned reactive astrogliosis, as a result of which the astrocytes hypertrophy and

lengthen their processes. The reason should be sought, probably, in the dysregulation of individual genes, including those responsible for the synthesis of GFAP and ALDH1L1 and similar proteins. Although for a long time it was believed that the appearance of such astrocytes is an indicator of pathology in the brain, today we can say for sure that reactive astrogliosis is an established protective and adaptive mechanism associated with increased reliability of the blood – brain barrier, increased trophic neurons, suppression of excitotoxicity of glutamate, and the most interesting in our opinion is the restriction of the processes of oxidative stress and neuroinflammation of various etiologies [30].

Accumulating evidence has shown that astrocytes do not just support the function of neurons, but play key roles in maintaining the brain environment in health and disease. Contrary to the traditional understanding of astrocytes as static cells, reactive astrocytes possess more diverse functions and phenotypes than previously predicted. In the present focused review, we summarize the evidence showing that astrocytes are playing profound roles in the disease process of amyotrophic lateral sclerosis. Aberrantly activated astrocytes in amyotrophic lateral sclerosis rodents express microglial molecular markers and provoke toxicities to accelerate disease progression. In addition, TIR domain-containing adapter protein-inducing interferon-β-dependent innate immune pathway in astrocytes also has a novel function in terminating glial activation and neuroinflammation. Furthermore, heterogeneity in phenotypes and functions of astrocytes are also observed in various disease conditions, such as other neurodegenerative diseases, ischemia, aging and acute lesions in the central nervous system. Through accumulating knowledge of the phenotypic and functional diversity of astrocytes, these cells will become more attractive therapeutic targets for neurological diseases [31].

1.1 Astrocytes and Alzheimer's disease. New ways to resolve neuroinflammatory processes in the brain

The incident of the death of Albert Einstein in 1955 at Princeton Hospital, pathologist Thomas Harvey removed the brain for examination, as is customary during an autopsy, but instead of leaving it to science, Harvey took the brain for himself. The scientist hoped that cytoarchitectonics would provide useful information about the correlation between neuroanatomy and genius. Scientific studies have found an increase in the number of astrocyte neuroglial cells and the phenomenon of astrogliosis in the brain of the great scientist, which is observed in patients with Alzheimer's disease, which tells that this is about pathology.

Alzheimer's disease is a neurodegenerative disorder characterized by beta-amyloid peptide (Aß) deposition, tau protein hyperphosphorylation, and neuroinflammation. Using positron emission tomography using the radioligand(11C)DEK, it was found that the enzyme monoamine oxidase-B (MAO-B) expressed by reactive astrocytes corresponds to the level of expression of two established markers of astrogliosis, GFAP and vimentin, during the progression of the pathology, and their number increased with age. This is probably a consequence of the abundant formation of Aß plaques and neuroinflammation in general. Although this analysis does not measure the overall extent of astrogliosis in the late stages of Aß accumulation, it gives doctors hope that with this study we will be able to detect changes in MAO-B in the early stages of Alzheimer's disease progression [31,32].

Proliferation and activation of microglia in the brain, concentrated around amyloid plaques, is a prominent feature of Alzheimer's disease. Human genetics data point to a key role for microglia in the pathogenesis of Alzheimer's disease. The majority of risk genes for Alzheimer's disease are highly expressed (and many are selectively expressed) by microglia in the brain. There is mounting evidence that microglia protect against the incidence of Alzheimer's disease, as impaired microglial activities and altered microglial responses to β-amyloid are associated with increased Alzheimer's disease risk. On the other hand, there is also abundant evidence that activated microglia can be harmful to neurons. Microglia can mediate synapse loss by engulfment of synapses, likely via a complement-dependent mechanism; they can also exacerbate tau pathology and secrete inflammatory factors that can injure neurons directly or via activation of neurotoxic astrocytes. Gene expression profiles indicate multiple states of microglial activation in neurodegenerative disease settings, which might explain the disparate roles of microglia in the development and progression of Alzheimer's disease pathology.

Postmortem analysis of brain tissue in patients with Alzheimer's disease revealed dysregulation of the activity of cyclin-dependent kinase 5 (Cdk5), synthesized by astrocytes, playing a significant role in neuron differentiation, neurotransmission, synaptogenesis and apoptosis of nerve cells. Recent studies have demonstrated the critical function of Cdk5 in the pathogenesis of Alzheimer's disease, as a regulator of the inflammatory response, and making astrocytic kinase a potentially new target for pharmacological intervention in Alzheimer's disease [33].

The astroglia-secreted protein thrombospondin-1 (TSR1) plays a crucial role in stimulating the formation of synapses. It is known that diabetes mellitus (with its inherent chronic hyperglycemia) leads to cognitive dysfunctions associated with inhibition of TSR-1 secretion in astrocytes, which leads to a decrease in the production of synaptic proteins. The new anti-diabetes drug rosiglitazone (RG), which is currently undergoing clinical trials, demonstrates anti-inflammatory properties in various brain pathologies. It is possible that in the near future RG will be used as a modulator of neuroinflammation resolution [34].

Researchers do not stop looking for drugs that can have a neuroprotective effect in the pathologies of Alzheimer's disease, vascular dementia, Parkinson's disease and others. The results of recent studies on the preparation safflower yellow(SY), present in Chinese folk medicine, demonstrate its ability to suppress oxidative processes, apoptosis of neurons, hyperphosphorylation of tau protein, as well as reduce the Aß and hyperactivation of astrocytes. Treatment of mice with the Alzheimer's disease-induced model significantly reduced Aß levels and increased the expression of enzymes associated with amyloid clearance in cells. Thus, SY may be very promising in a therapeutic approach for the resolution of Alzheimer's disease [35,36].

1.2 Astrocyte Transplantation and the Melatonin Effect

The driving force behind today's explosive development of medicine is, in particular, quantum theory and the computer revolution. The first made it possible to describe models of molecular structures in amazing detail, and gene sequencing made it possible to find mutations responsible for the development of a particular disease. Against the backdrop of these two, scientists are getting closer to applying astrocytic cell technology. The recognition that astrocyte dysfunction plays almost the main role in a wide range of neurological disorders makes us think about therapeutic astrocyte transplantation in the treatment of the affected human CNS. It has long been known that the astroglial scar tissue of the affected areas of the brain and spinal cord suppresses the regeneration of neuronal axons [36].

In particular, the work of scientists from the University of Colorado, who have made impressive progress in restoring injuries to the central nervous system in mice by transplanting generated human astrocyte progenitor cells in combination with recombinant decorin (hr-decorin), which suppresses the inflammatory response in nervous tissue, suggests that this practice may be revolutionary. Previously, in the treatment of spinal injuries, it was believed that any attempt to restore the nerves would cause severe pain and suffering. However, Steven Davis and his team found that when using some types of astrocytes, regeneration is effective and painless, while other types of astrocytes do not produce results at all. In this regard, it is logical to assume that such a technique of transplanting astrocyte progenitor stem cells will be useful in the treatment of stroke, Alzheimer's and Parkinson's diseases. When analyzing the current literature and the latest developments in this field, we cannot ignore the effect of melatonin on the proliferation and differentiation of neural stem cells, which are self-healing, pluripotent and undifferentiated cells [37,38].

NSC therapy for tissue regeneration can be a promising therapy, but there is a problem – the low survival rate of transplanted cells associated with the development of inflammation, the culprit of which is mostly IL-18. The powerful antioxidant melatonin has a beneficial effect on NSCs and is an IL-18 antagonist. All inhibitory effects of IL-18 on NSCs were significantly reduced with melatonin treatment. In addition, melatonin stimulated the production of neurotrophins (BPNF) and (GDNF) derived from astroglial cells. Note that if the synthesis of neurotrophins is artificially inhibited, the opposite negative effect occurs for the protective properties of melatonin on the NSC. The findings suggest that melatonin may play an important role in promoting the survival of NSCs in neuroinflammatory processes. The antinociceptive mechanism of melatonin in the implementation of anti-

inflammatory and antiallodial effects, in which the synthesis of inflammatory mediators (IL-1, IL-6, IL-8, TNF-α and chemokine RANTES) is inhibited, has also been proven [39,40].

2. CONCLUSION

Astrocytes and other cellular elements of glia in the central nervous system have multidirectional functions that contribute to both the survival of neurons and their delayed damage. Astroglial reactivity is manifested by the ability of astrocytes to repair various CNS lesions. However, a glial scar consisting of activated astrocytes can determine various neurotoxic effects that inhibit the repair of neurons and the regeneration of axons. In ischemia, traumatic brain injury, or neurodegenerative diseases, astrogliosis may be modulated. Understanding the importance of astrocytes in the mechanisms of repair and damage to brain cells in various forms of CNS pathology determines the possibility of targeted search for drugs that affect the rate of development of reactive astrogliosis in response to various brain injuries. At the same time, pharmacological modulation of activated astrocytes and other components of glia can be an integral part of the therapy of neurological diseases.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICS APPROVAL

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Authors have declared that no competing interests exist.

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