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Review

An emerging role of astrocytes in aging/neuroinflammation and gut-brain axis with consequences on sleep and sleep disorders

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ABSTRACT

Understanding the role of astrocytes in the central nervous system has changed dramatically over the last decade. The accumulating findings indicate that glial cells are involved not only in the maintenance of metabolic and ionic homeostasis and in the implementation of trophic functions but also in cognitive functions and information processing in the brain. Currently, there are some controversies regarding the role of astrocytes in complex processes such as aging of the nervous system and the pathogenesis of age-related neurodegenerative diseases. Many findings confirm the important functional role of astrocytes in age-related brain changes, including sleep disturbance and the development of neurodegenerative diseases and particularly Alzheimer's disease. Until recent years, neurobiological research has focused mainly on neuron-glial interactions, in which individual astrocytes locally modulate neuronal activity and communication between neurons. The review considers the role of astrocytes in the physiology of sleep and as an important "player" in the development of neurodegenerative diseases. In addition, the features of the astrocytic network reorganization during aging are discussed.

1. Introduction

The last decade has significantly reconsidered the role of glial cells, particularly astrocytes, in the functioning of the central nervous system (CNS). The accumulating findings indicate that astroglial cells are involved not only in the maintenance of metabolic and ionic homeostasis and the implementation of trophic functions (Volterra and Meldolesi, 2005) but also in cognitive functions and information processing in the brain (Kol et al., 2020; Verkhratsky and Nedergaard, 2018). Astrocytes, connecting through gap junctions, form astroglial networks, using modulating and supplying neurons with metabolic substrates. In recent years, studies have revealed the role of disorders of astroglial interactions in pathological lesions of the nervous system. Morphological and functional remodeling of astrocytic networks as a result of aging, pathologies, or exposure to stress factors is of great interest (Charvériat et al., 2017; Ridet et al., 1997). Numerous experimental and clinical studies indicate the importance of astrocytes in the development of many CNS pathologies, including neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) (Smethurst et al., 2020), Parkinson's disease (PD) and Alzheimer's disease (AD) (Habib et al., 2020).

One of the key factors in the brain's normal aging, as well as the development of age-related pathologies of the nervous system, is neuroinflammation (Calabrese et al., 2018). Activation of astrocytes as well as microglia and their interaction underlies inflammatory responses (Colombo and Farina, 2016). However, the exact mechanisms of this interaction remain to be elucidated.

Of particular interest is the contribution of external factors, including the state of the intestinal microflora and the quality of sleep, to the development of neuroinflammation and, as a result, pathological disorders of the nervous system. The contribution of external factors to the pathogenesis of neurodegenerative diseases is of great interest since a number of modern works consider the important role of both microglia and astrocytes in the neuroinflammatory response observed in dysbacteriosis and sleep deprivation (Morais et al., 2021; Pak et al., 2020). Microglia and astrocytes in the glymphatic system (GS) become promising objects for studying the systemic relationship of cellular aging, dysbacteriosis, sleep disorders, and inflammation with brain aging.

The regulation of sleep, a critical and important process for the

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normal functioning of the CNS system, is another important and interesting function of astroglia. Changes in the sleep profile seen in people with age are usually part of normal aging. However, sleep disturbances are common in patients with neurodegenerative diseases such as AD, PD, ALS, and Huntington's disease. Therefore, sleep profile changes can be considered an early diagnostic sign of neurodegenerations. It has been shown that astrocytes are involved in both homeostatic and circadian regulation of the sleep process and can be considered as a potential therapeutic target for sleep disorders (Bojarskaite et al., 2020; Haydon, 2017; Vaidyanathan et al., 2021).

Our understanding of the role of astrocytes in the CNS has changed dramatically over the past decade. Currently, there are disputes about the role of astrocytes in such complex processes as sleep, aging of the nervous system, and pathogenesis of age-related neurodegenerative diseases. These contradictions must be resolved. This review will consider the features of the reorganization of the astrocytic network during aging. In particular, we consider the contribution of astroglia to neuroinflammation as the main factor in the development of age-related CNS pathologies. In addition, the role of astrocytes in the physiology of sleep and the development of sleep disorders will be discussed.

1.1. Physiological characteristics of astrocytes

Astrocytes are one of the most common cell types in the CNS (~20–40% of all glial cells) (Giovannoni and Quintana, 2020; Pelvig et al., 2008). In the human cortex, there are approximately 1.4 astrocytes per neuron; however, the neuron/astroglia ratio may vary depending on the region of the CNS (Nedergaard et al., 2003; von Bartheld et al., 2016). In the brain gray matter, astrocytes form multiple contacts with neuronal membranes, including synaptic regions. Astrocytes surround about 60% of the axonic dendritic synapses in the hippocampus. Human astrocytes can contact up to $2 \bullet 10^6$ synapses (Bushong et al., 2002; Oberheim et al., 2009).

Interactions between astrocytes are based on gap junctions of adjacent cell membranes (Bennett et al., 2003). Astrocytic gap junctions function in the transport of ions (Scemes et al., 2000), metabolites (Mese et al., 2007), and neuromodulators (Ribeiro et al., 2002), which mediate signal transmission in the network (Vasile et al., 2017). The gap junction structure is formed by the interaction of connexons on adjacent cells. Each connexon consists of six connexin protein molecules. Eleven different connexins are expressed in the brain. Connexin 30 (Cx30) and connexin 43 (Cx43) mainly provide communication between astrocytes. Astrocytes also express pannexin-1 (Panx-1), which forms channels with characteristics similar to connexin hemichannels (Panchina et al., 2000). Interastrocytic gap junctions are structures essential for the intercellular transfer of metabolites, gliotransmitters (ATP, glutamate, D-serine, etc.), and ions (Ca^{2+}, K^+, Na^+) (Halassa and Haydon, 2010). Wave-like Ca^{2+} transfer between astrocytes is one of the interesting functional features of these cells, realized through gap junctions. Astrocytes calcium signaling is known to be an important factor for CNS homeostasis (Parpura and Verkhratsky, 2012; Semyanov et al., 2020).

Another functional feature of astrocytes is spatial potassium buffering, which is the ability to redistribute local increases in the extracellular K^+ concentration due to neuronal activity. Astrocytes have a high density of potassium channels (Kir4.1) to provide local buffering and further redistribution of potassium ions through gap junctions. Such buffering is essential for the further excitability of the neuronal membrane. (Wallraff et al., 2006).

Astrocytes, together with microvascular endotheliocytes, pericytes, microglia, neuropil, and intercellular space, form the NVU (neurovascular unit) that ensures the functioning of the BBB (blood-brain barrier), the most important highly selective system that implements the transport of substances from the bloodstream and provides homeostasis of the CNS (Troili et al., 2020). Astrocytes can act as a functional mediator between neuronal synapses and blood vessels, interacting *via* end feet processes with the walls of nearby arterioles. These perivascular endfeet of astrocytes are important and highly specialized cellular compartments with a high density of astrocyte-specific proteins such as aquaporin-4 (AQP4) water channels, Cx43, purinergic receptors, and potassium channels (Simard et al., 2003). Equally important is the role of astrocytes in the GS, which is a system of perivascular channels around the blood microvessels of the brain, formed by astroglial processes with a high density of AQP4 that ensure the flow and filtration of cerebrospinal fluid through the brain parenchyma, as well as the effective removal of soluble proteins and metabolites from the CNS (Jessen et al., 2015). Notably, the GS may also play a role in the clearance of tau proteins and amyloid-beta (Aβ) aggregates (Iliff et al., 2012; Rasmussen et al., 2018; Simon et al., 2018).

Astrocytes play a unique role in the energy metabolism of the brain and in meeting the energy requirements of active neurons. The brain represents only 2% of the total body mass but has an intense energy metabolism. The brain consumes more than 20% of oxygen and about 25% of glucose consumed by human body (Bélanger et al., 2011). The entire surface of the brain's capillaries is covered with astrocytes endfeet, which form a cellular barrier for the distribution of incoming glucose. While glucose is generally accepted as the brain's energy source, the form in which glucose is taken up by neurons is the subject of intense debate. The main putative mechanism of the interconnection between neurons and astrocytes, mediated by the transfer of nutrients and neurotransmitters, is the glucose-lactate shuttle (ANLS). According to the ANLS, activity-induced glucose uptake occurs predominantly in astrocytes, which metabolize glucose anaerobically. Lactate produced from anaerobic glycolysis in astrocytes is then released from astrocytes and provides the primary metabolic fuel for neurons. The activity of the anaerobic oxidation process in astrocytes and the transfer of lactate through monocarboxylate transporters to neurons is directly dependent on the release of glutamate (the main excitatory neurotransmitter) by neurons. Glutamate is transported inside astrocytes together with Na^+ ions, which leads to an increase in the concentration of sodium ions inside astrocytes and activation of Na^+/K^+-ATPase. Activation of Na^+/K^+-ATPase stimulates glycolysis, i.e., glucose utilization and lactate production by astrocytes. Finally, the most important function of astroglia is the regulation of neurovascular communication.

Moreover, several major astrocyte-mediated mechanisms of vasoregulation have been reported. Among the early works, Paulson and Newman proposed the concept according to which the influx of K^+ into astrocyte endings near active synapses and an outflow of K^+ from the endfeet of astrocytes, a mechanism of K^+-dependent vasodilation known as potassium "siphoning" by astrocytes (Bekar and Nedergaard, 2013; Paulson and Newman, 1987). Activation of synaptic transmission leads to a Ca^{2+} influx into the astrocyte terminal processes, which promotes the exocytosis of vasoactive substances in the areas of astrocytic terminals (MacVicar and Newman, 2015; Muñoz et al., 2015). These substances include epoxyeicosatrienoic acid (20-HETE), which is derived from arachidonic acid synthesized by astrocytes and has vasoconstrictive activity, and prostaglandin E2 (PGE2), which has vasodilating activity (Anderson and Nedergaard, 2003; Metea and Newman, 2006; Mulligan and MacVicar, 2004; Zonta et al., 2003).

1.1.1. Heterogeneity of astrocytes

Human astrocytes demonstrate morphological, molecular, developmental, physiological heterogeneity, and heterogeneity of transcriptional profile (Pestana et al., 2020). Heterogeneity plays a fundamental role in understanding the role of astrocytes in brain function and neurodegeneration processes. Nevertheless, astrocytes morphological and functional heterogeneity and their role in the development of pathologies are the subjects of research worldwide.

Inflammatory (neurotoxic) astrocytes (A1), one of the first described subtypes of reactive astrocytes, are present in various neurodegenerative diseases; however, their role in the pathogenesis of these diseases is not fully understood yet. Moreover, these cells experimental genetic and therapeutic correction reduces the rate and degree of

neurodegeneration. In addition to the inflammatory reactive astrocytes, a second subtype has been identified: neuroprotective astrocytes (A2). However, a recent report by Escartin et al. revealed the disadvantages of the binary classification of astrocytes (Escartin et al., 2021).

Based on morphology, four types of astrocytes have been described in the adult cerebral cortex: interlaminar astrocytes, protoplasmic astrocytes, varicose projection astrocytes, and fibrous astrocytes (Elston et al., 2009). These subtypes are distinguished based on glial fibrillary acidic protein (GFAP), astrocytes major intermediate filament protein. However, identifying astrocytes based solely on GFAP expression would bias research towards a specific subpopulation and would not improve our understanding of astrocytes (Verkerke et al., 2021).

Developments in single-cell transcriptomics have extended our understanding of the heterogeneity of this cell type beyond the original binary classification of inflammatory and neuroprotective astrocytes (Reid and Kuipers, 2021). Several unique clusters of reactive astrocytes have been identified in autoimmune diseases (Wheeler et al., 2020) and AD (Habib et al., 2020).

Transcriptomic studies have identified five subtypes of astrocytes in the cortex and hippocampus of adult mice (AST1–5). There is a clear division of subtypes between the cortex and the hippocampus: AST1 and AST4 are predominantly hippocampal, AST2 are predominantly cortical, and AST3 and AST5 are evenly distributed between brain regions (Batiuk et al., 2020). Each subtype has its metabolic characteristics and can be involved in various processes of brain functioning. The morphological heterogeneity of astrocytes in different brain parts has also been shown. Striatal and hippocampal astrocytes differ in their territory size, the number of neuronal somata they contact, the number of synapses within a territory, and the proximity of astrocyte processes to excitatory synapses. It has been shown that regional heterogeneity of astrocytes underlies different responses to the treatment of bacterial infections, stroke, and possibly Norri's disease (Miller et al., 2019).

In addition, a recent study showed that neurons are involved in the specialization of astrocytes. Garcia et al. (2010) found the expression of the transcription factor Gli1 by a subpopulation of adult brain cortical astrocytes, which indicated the activity of the Sonic hedgehog (Shh) signaling pathway in these cells . It is assumed that the expression of the Sonic hedgehog (Shh) gene secreted by deep cortical neurons contributes to the specialization of astrocytes molecular and functional features during the morphofunctional development of the astrocytic network (Hill et al., 2019; Xie et al., 2022). A recent study by Miller et al. (2019) identified the population of astrocytes demonstrating enrichment of the Shh pathway and the ability to regulate the density of dendritic spines in layer V cortex neurons by norrin secretion. Thus, the detected functional heterogeneity of astrocytes indicates a possible role of astroglia in the pathogenesis of Norrie's disease.

1.1.2. Relationship between astrocytes and other cells

Until recent years, neurobiological research has focused mainly on neuron-glial interactions, in which individual astrocytes locally modulate neuronal activity and communication between neurons. According to this concept, astrocytes can modulate neuronal activity by secreting so-called gliotransmitters (Santello et al., 2012). These molecules are secreted into the intercellular space in various ways but mainly by exocytosis followed by vesicle binding to the target membrane and release through hemichannels. The main known gliotransmitters are ATP, glutamate, aspartate, D-serine, taurine, and homocysteine (Verkhratsky and Butt, 2013).

On the other hand, recent experimental findings suggest that astrocytes can form large astrocytic networks that facilitate the exchange of signaling molecules (Giaume et al., 2010), (Breithausen, 2020). This means that astrocytes might respond to external stimuli and develop a consolidated response independently of neurons.

Since astrocytes are not electrically excitable, the main manifestation of astrocytic network activity is the ability to produce and transmit Ca^{2+} signals, which can spread between cells as "calcium waves" (Newman and Zahs, 1997). A series of experiments on the effect of astrocytic networks on neuronal activity *in vitro* demonstrated that gap-junction blockade reduces the number of astrocytes generating spontaneous Ca^{2+} waves (Mitroshina et al., 2020; Shtrahman et al., 2017). It is also known that there is interastrocytic Na^{+} signaling which is formed in parallel with Ca^{2+} waves (Felix et al., 2020; Parpura and Verkhratsky, 2012). Glutamate released by a Ca^{2+}-dependent mechanism is taken up by the Na^{+}/glutamate cotransporters, resulting in the undulating propagation of cytosolic Na^{+} (Bernardinelli et al., 2004; Kirischuk et al., 2012).

The proximity of astrocytic processes to synaptic contacts and receptors for neurotransmitters on the astrocyte membranes led to the hypothesis of a tripartite synapse, according to which synapses consist of three equally important parts: the presynaptic ending, the postsynaptic membrane of the neuron, and the surrounding astrocyte (Araque et al., 1999; Halassa et al., 2007; Santello et al., 2012) (Fig. 1.). Later, the concept of the tripartite synapse was transformed into the multipartite synapse theory. According to this theory, the structure of the synapse is represented by the following elements: pre- and postsynaptic membranes of neurons, an astrocyte process, a microglial cell process, and an extracellular matrix (Verkhratsky and Nedergaard, 2014). Finally, the concept of an active brain environment that unites all components of the nervous tissue (neurons, glia, extracellular matrix, and vascular network) into a single system is reported (Semyanov and Verkhratsky, 2021).

The relationship between astrocytes and microglia in the development of neuroinflammation is noteworthy (Liu et al., 2020). Microglia can regulate excitatory neurotransmission by rapidly producing small amounts of ATP, which signals astrocytes for ATP synthesis and

BOX: Contribution of astrocytes to neuroinflammation; reactive astrogliosis

Functional alteration of astrocytes primarily involves a change in the level of astrocyte synthetic activity, called reactive astrogliosis. Accordingly, astrocytes with increased synthetic activity are referred to in the literature as "reactive astrocytes". Reactive astrocytes proliferate, become hypertrophied, increase the expression of intermediate filament proteins, cytokines, and chemokines, and cluster into polarized bundles around the damaged area. Polarized astrocytes combine with extracellular matrix (ECM) components to form a scar that separates the damaged area from adjacent healthy tissue (Cekanaviciute and Buckwalter, 2016). Reactive astrogliosis is a response to stress, including ischemia, trauma, and neuroinflammation, and is also observed in neurodegenerative diseases (Eddleston and Mucke, 1993; Pekny and Nilsson, 2005). Astrocyte reactivity includes differential expression of more than 1000 genes, some of which are collectively associated with inflammation (Escartin et al., 2021; Zamanian et al., 2012).

It has been shown that local (non-interacting) networks of reactive astrocytes can start interacting (Oberheim et al., 2009). Recently, much attention has been paid to studies of the role of astroglia in the processes occurring during brain aging and various age-related neurodegenerative diseases, particularly AD (Palmer and Ousman, 2018).

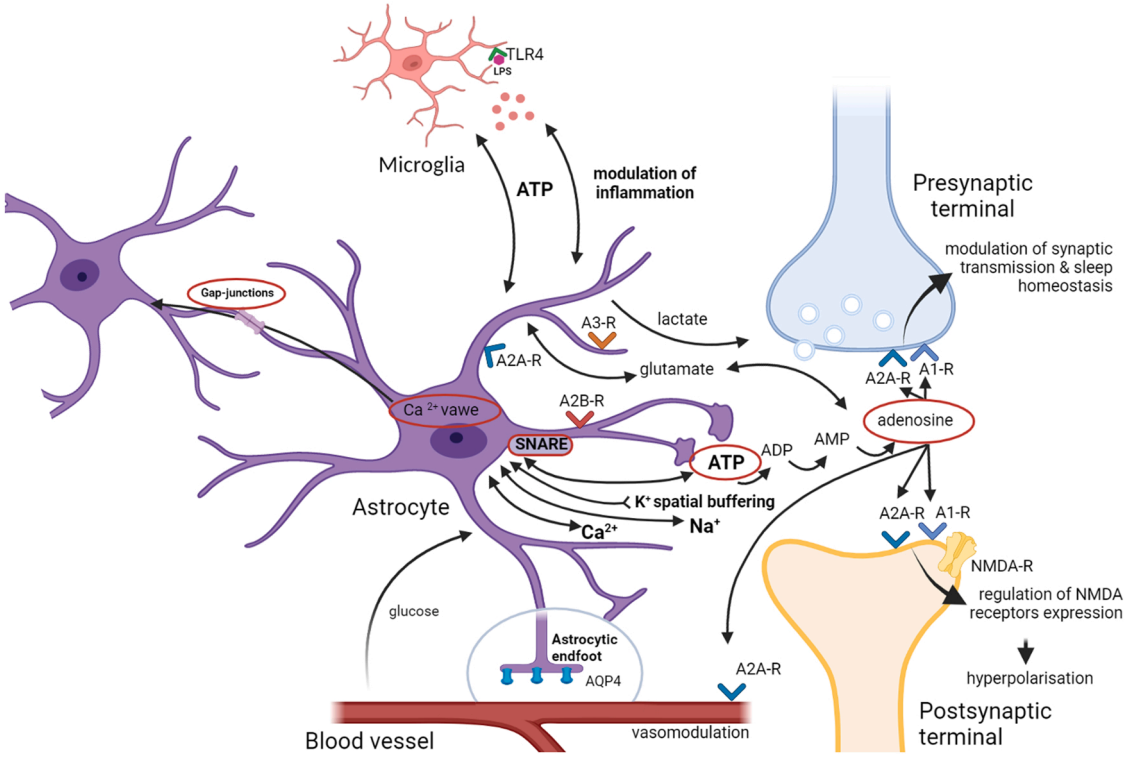

Fig. 1. A simplified scheme of synapse with a focus on the basic ways of astrocyte-mediated regulation. Abbreviations: A1-R, A2A-R, A2B-R, A3-R, adenosine receptor type. NMDA-R, N-methyl-D-aspartate receptors. ATP, adenosine triphosphate. ADP, adenosine diphosphate. AMP, adenosine monophosphate. SNARE, soluble NSF attachment receptor.

glutamate exocytosis, thereby enhancing synaptic transmission through metabotropic glutamate receptors (Pascual et al., 2012). Several studies show that some astrocyte functions are regulated by prior microglia activation (Achour and Pascual, 2010; Liu et al., 2020; Pascual et al., 2012). In a recent *in vivo* study using a murine transgenic AD model (5xFAD and 3xTg-AD), Park et al. (2021) noted preservation of neuronal viability and improvement of spatial learning and memory when microglia-mediated astrocyte activation was blocked by subcutaneous administration of NLY01 (pegylated exendin-4, a long-acting GLP-1R agonist).

One mode of intercellular interaction (*e.g.*, between nerve cells) is the formation of extracellular vesicles (EVs) (Horn and MacLean, 2021). There are various types of EVs of different sizes and functions, but the most studied are exosomes, microvesicles, and apoptotic bodies. Some experiments have demonstrated that the BBB is highly permeable to EVs. In one study, EVs were isolated from the plasma of rats exposed to lipopolysaccharides or subjected to partial hepatectomy. Intracerebroventricular or peripheral injection of these EVs into other rats led to the release of proinflammatory cytokines in the cerebrospinal fluid (Fricke et al., 2020). This indicates that EVs in the blood not only cross the BBB but also cause neuroinflammation in the brain. Similarly, in a model of traumatic brain injury, microglia released increased amounts of EVs, which caused neuroinflammation when administered to normal animals (Kumar et al., 2017).

It has also been shown that activated microglia release higher numbers of EVs (Aires et al., 2021; Bianco et al., 2005), which can activate naive glial cells (Verderio et al., 2012). In addition, Beneventano et al. (2017) found that EVs from activated microglia have different effects on neurotoxicity depending on the source of microglial activation.

1.1.3. Sex differences in astrocytes in response to pathological influences

It is interesting to note that astrocytes exhibit sex differences in numbers, differentiation, and function. About 27.9 billion glial cells are found in the neocortex of the female brain and 38.9 billion in the male (Pelvig et al., 2008), ~20–40% of which are represented by astrocytes (Blinkow and Glezer, 1968).

Numerous studies noted differences in the reactive changes in "male" and "female" astrocytes in response to pathological influences (Chowen and Garcia-Segura, 2021) (Fig. 2). In particular, a difference in astrocyte reaction to the exogenous effect of factors *in vitro* (for example, bacterial lipopolysaccharides (Chistyakov et al., 2018; Loram et al., 2012; Santos-Galindo et al., 2011), as well as oxygen-glucose deprivation was noted. Besides, sex differences in astroglial response were demonstrated when modeling pathologies *in vivo*. For example, "female" astrocytes of newborn rats demonstrate enhanced mitochondrial metabolism immediately after neonatal hypoxia-ischemia *in vivo* compared to "male" astrocytes; however, the recovery rate of "male" astrocytes is higher (Morken et al., 2014). Moreover, Morrison and Filosa reported a difference in the calcium response of astrocytes to carotid artery occlusion in adult mice. Females ipsilateral astrocytes were found to exhibit a higher frequency of Ca^{2+} elevations than males (Morrison and Filosa, 2016). In general, "male" astrocytes show lower resistance to oxidative stress (Liu et al., 2008; Morizawa et al., 2012; Morrison and Filosa, 2016). *In vitro* experiments on primary prenatal astrocytic cultures of mice showed that astrocytes obtained from the brain of a female with an injection of testosterone propionate (100 μg) respond to inflammatory processes in the same way as primary astrocytes obtained from males, suggesting that perinatal administration of testosterone affects the change in astrocyte reaction to pathological conditions (Santos-Galindo et al., 2011). Also, when Aβ 1–40 was added to the culture medium with astrocytes obtained from a female rat, a more pronounced pro-inflammatory response compared to astrocytes isolated from a male brain was found (Lennol et al., 2021).

A number of studies demonstrate sexual dimorphism in predisposition to certain neurodegenerative diseases, such as AD (Dubal, 2020; Ferretti et al., 2018; Fisher et al., 2018), which women are more susceptible to, as well as PD with a higher prevalence in men

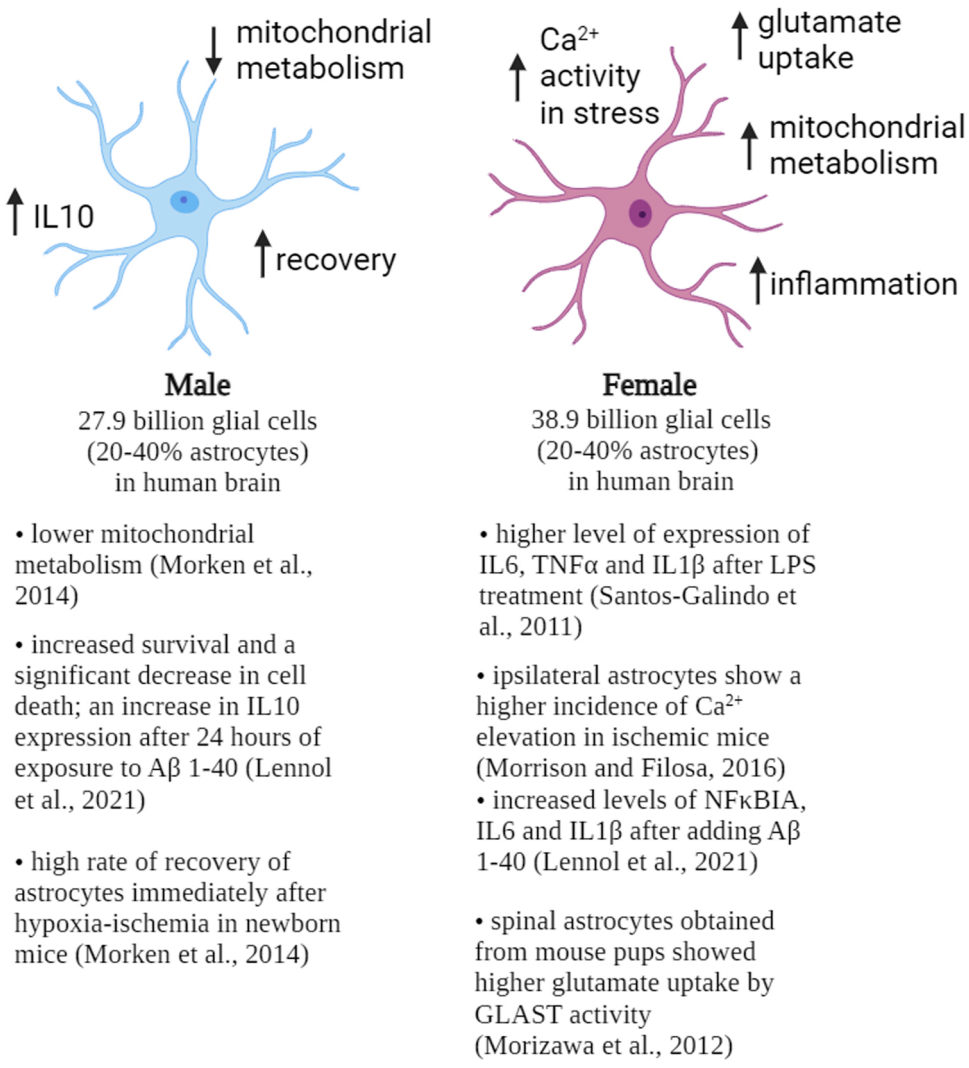

Fig. 2. Sex differences in responses to pathological influences on astrocytes in males and females. Aβ, amyloid-beta. IL, interleukins. TNFα, tumor necrosis factor alpha. LPS lipopolysaccharides. GLAST, high-affinity glutamate/aspartate transporter.

(Jurado-Coronel et al., 2018; Meoni et al., 2020). Sex differences in the prevalence, as well as clinical features of the course of the pathology, were identified for Huntington's disease (Meoni et al., 2020), epilepsy (Christian et al., 2020), multiple sclerosis (Schwendimann and Alekseeva, 2007), and the number of other pathologies of the nervous system. Sex differences at the level of cell reaction in response to stress, particularly astroglial reactions, are of great interest.

1.1.4. Astrocytes and the gut microbiota-brain axis

Interestingly, a gut microbiota—brain axis has been described in some studies. Alterations in the composition of the microbiota, as well as dysbacteriosis, were found to contribute to several neurodegenerative diseases such as AD (Cattaneo et al., 2017; Friedland and Chapman, 2017; Mayer and Tillisch, 2011; Sharon et al., 2016; Sun et al., 2020), PD (Hopfner et al., 2017), and ALS (Rowin et al., 2017). Giovannini et al. (2021) summarized the available data on the impact of the waste products of the intestinal microbiota on astrocyte-mediated and microglia-mediated regulation of neuronal functioning. Recent studies have revealed dysbacteriosis in patients with neurodegeneration (Castelli et al., 2021; Kesika et al., 2020; Koszewiczz et al., 2020), as well as an imbalance of intestinal microflora in the APP/PS1 mouse model of AD (Harach et al., 2017).

The role of astrocytes and microglia (Mossad and Blank, 2021) in the regulation of the gut microbiota—brain axis is of even greater interest (Fig. 3). In mice without microbiota (germ-free mice), the expression of occludin and claudin-5 is reduced, tight intercellular junctions are disorganized, and permeability of the interstitial barrier (IB) and BBB is increased (Braniste et al., 2014; Hayes et al., 2018). Microbiota products, mainly butyrate, maintain the integrity of these barriers (Hoyles et al., 2018). Indeed, intestinal recolonization of germ-free mice by microbiota increased the expression of gap junction proteins and promoted the restoration of BBB integrity (Braniste et al., 2014). Disruption of the BBB, NVU, and GS causes a decrease in transport and results in ineffective removal of toxic substances that can accumulate in the brain parenchyma and lead to neuroinflammation and consequent tissue damage (Abbott, 2002; Sweeney et al., 2018a; Zhu et al., 2007). It is known that activated astrocytes (astrocytes A1) express and secrete cytokines that disrupt BBB permeability (Abbott, 2002) and activation (astrogliosis) of perivascular astrocytes, causing depolarization of AQP4, which can ultimately lead to both vascular and glymphatic dysregulation and disorganization of the BBB. These inflammatory processes are considered one of the early stages of AD pathogenesis (Iturria-Medina et al., 2016; Sweeney et al., 2018b).

Noteworthy, that the gut microbiota can modulate the activity of astrocytes that metabolize dietary tryptophan with the formation of natural ligands for aryl hydrocarbon receptors (AHR), including indole-3-aldehyde and indole-3-propionic acid, which bind to astrocyte AHR (Rothhammer et al., 2016; Zelante et al., 2013). Another reported

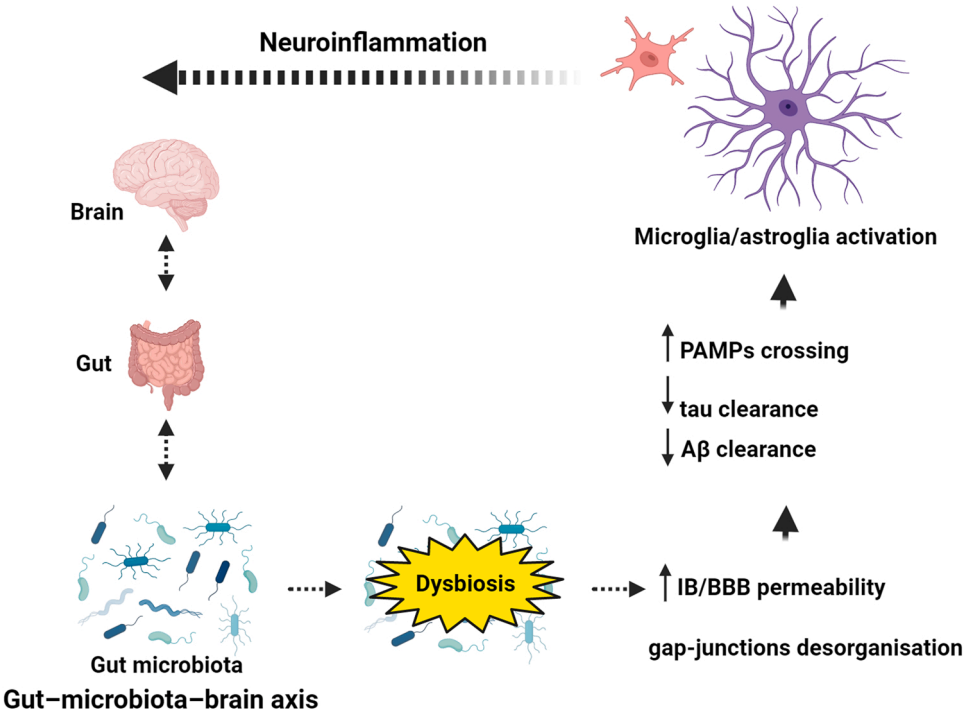

Fig. 3. The role of astrocytes and microglia in the regulation of the gut microbiota–brain axis. Abbreviations: PAMPs, pathogen-associated molecular patterns. IB, interstitial barrier. BBB, the blood-brain barrier.

example of astrocytic modulation by gut microbiota is activation by the Gram-negative bacteria *Porphyromonas gingivalis*, one of the main pathogenetic causes of chronic periodontitis, leads to an increase in cytokine production, inflammatory brain lesions, and cognitive impairment (Zhang et al., 2018).

It is important to note the critical role of microglia in neuroinflammation. Several hypotheses suggest how cellular microbiota affect microglia: (1) ingress of bacterial metabolites, including short-chain fatty acids (SCFAs) through the BBB; (2) migration of immune cells expressing SCFA receptors; (3) migration of immune cells after interaction with SCFA through the BBB; (4) penetration of microbe-associated molecular patterns (MAMPs) produced by the microbiota through the BBB, followed by exposure to microglia. Moreover, peripheral macrophages recognizing MAMPs might migrate through the BBB, and intestinal microbiota can directly bind to the resident CNS microglia *via* the *vagus nervus* (Abdel-Haq et al., 2019). Several molecules, including bacterial lipopolysaccharides, peptidoglycans, and PAMPs (pathogen-associated molecular patterns) (Pandey et al., 2015), can cross the IB and BBB (Banks and Robinson, 2010; Vargas-Caraveo et al., 2017) to reach the brain parenchyma, where they can be recognized by membrane Toll-like receptors 4 (TLR4) of microglia (Zhang et al., 2015). Prolonged microglia activation may increase Aβ deposition in healthy neurons and phagocytosis of these neurons (Brown and Neher, 2014; Neher et al., 2012; Vilalta and Brown, 2018), thereby enhancing neurodegeneration (Deleidi et al., 2015; Giunta et al., 2008).

All the above leads us to two conclusions. First, astrocytes play an active role in the brain's aging process and the development of age-related neurodegenerative diseases, particularly AD. Second, exposure to products of bacterial microbiota can contribute significantly to the activation of astrocytes and microglia and affect their roles in neuroinflammation and the development of nervous system pathologies. However, this topic is still in its infancy and requires further detailed study.

The following issues remain open for discussion and further study: (1) the connection of microbiota with innate immunity cells in the CNS, as well as with microglia; (2) the phenotypic changes that occur in the cell populations in the CNS during dysbacteriosis; (3) how the interactions of the aging of microglia and astrocytes with the gut microbiota regulate various processes in healthy and diseased brains. Finally, a more in-depth research on the mechanisms of interaction between gut microbiota and brain glia is required.

1.1.5. The role of astrocytes in brain aging/neuroinflammation

1.1.5.1. Morphological changes in aging astrocytes. Aging is associated with morphological and functional remodeling of astrocytes with a prevalence of morphological atrophy and loss of function. In particular, aging is associated with a decrease in astroglial synaptic coverage, deficiency in glutamate and potassium clearance, reduced astroglial synthesis of synaptogenic factors such as cholesterol, decrease in AQP4 channels in astroglial endfeet followed by a decline in the glymphatic clearance, decrease in astroglial metabolic support via the lactate shuttle, decrease in adult neurogenesis resulting from the reduced proliferative capacity of radial stem astrocytes, decline in the astroglial-vascular coupling and low blood-brain barrier, and decrease in astroglial ability to mount reactive astrogliosis (Verkhratsky et al., 2021).

It is generally accepted that physiological aging is not associated with any significant decrease in the number of astroglial cells across CNS regions. The number of astrocytes in the human brain does not change with age and remains unchanged even in centenarians (Pelvig et al., 2008).

Data on the morphological appearance of astrocytes in old brains are also contradictory: various studies have reported both increases and decreases in the size and complexity of astrocytes (Bondi et al., 2021). It should be noted that most morphological studies have been performed on astrocytes immunostained for GFAP, which is not ideal as a morphological marker for a number of reasons (Verkhratsky et al., 2021). It has been confirmed that morphological changes occur in human astrocytes with age and are manifested in the shortening and thickening of the processes (Cerbai et al., 2012; Jyothi et al., 2015; Kanaan et al., 2010). It has also been confirmed that this age-related change in astrocyte morphology occurs in aged rodents (Castiglioni

et al., 1991; Amenta et al., 1998) and primates (Kanaan et al., 2010; Robillard et al., 2016).

Changes in astrocytes during aging are multifaceted and region-specific. In the study of astrocytes in human substantia nigra pars compacta, there was a trend toward an increase in the soma size, which indicates the phenotypic switch over with aging (Jyothi et al., 2015). Using two-photon microscopy in conjunction with 3D reconstruction and Sholl and volume fraction analysis, Popov et al. recently demonstrated a significant reduction in the number and length of astrocytic processes in astrocytic territorial domains and astrocyte-to-astrocyte connections in aged mouse brains. Moreover, a patch clamp study of Ca^{2+} revealed deficits in K^{+} and glutamate clearance and a spatiotemporal reorganization of Ca^{2+} events in aged astrocytes. These changes occurred in parallel with the impairment of synaptic long-term potentiation in hippocampal CA1 neurons in aged mice (Popov et al., 2021).

1.1.5.2. Molecular and genetic changes in aging astrocytes. Among the changes at the molecular level, the expression of the glial fibrillary acidic protein (GFAP), used as a classic astroglial marker, was found to be increased in aging astrocytes (Clarke et al., 2018; Nichols et al., 1993; Wu et al., 2005). Since increased GFAP expression is one of the markers of synthetic astrocyte activity (Boisvert et al., 2018; Brenner and Messing, 2021; Clarke et al., 2018; Liddelow and Barres, 2017; Matias et al., 2019), the findings indicate that astrocytes increase their metabolic activity with aging and exhibit a senescence-associated secretory phenotype (SASP) (Fig. 4). Also, several other molecular markers specific to reactive astrocytes have recently been identified as additional molecular markers of aged astrocytes (Table 1, Supplementary), such as increased expression of GFAP, a serine protease inhibitor (*Serpina3n*) (Clarke et al., 2018) and lipocalin-2 (*Lcn-2*) (Lee et al., 2009). The expression levels of genes encoding factors C3 and C4B of the complement system (Boisvert et al., 2018; Clarke et al., 2018) and major histocompatibility complex I (MHC I) (Clarke et al., 2018), as well as genes involved in antigen presentation (H2-D1 and H2-K1) (Verkerke et al., 2021) also increase with brain aging. The manifestation of a proinflammatory phenotype by astrocytes, leading to abnormalities in their normal functioning in the CNS, may be one of the factors in the development of cellular aging, called "astrosenescence" (Cohen and Torres, 2019).

A comparison of the expression of phagocytic genes in astrocytes revealed that the expression of most genes involved in phagocytosis did not change with age. However, some phagocytic pathway genes, including *Pros1*, *Mfge8*, *Megf10*, and *Lrp1*, were significantly activated with age (Clarke et al., 2018). It is important to note that the expression of several histocompatibility molecules, such as *Megf10*, *Mertk* and *Lrp1*, may not be associated with the development of inflammatory responses since astrocytes can use these receptors to cleanse myelin residues produced in the brain during aging (Nag and Wadhwa, 2012; Rawji et al., 2020). Besides, MHC I expression increases with age in individuals without cognitive impairment but decreases in those with cognitive impairment (Lazarczyk et al., 2016).

In aging astrocytes, an impairment of the glutamate clearance system caused by a decrease in the expression of metabotropic glutamate receptors mGluR3 is found (García-Bea et al., 2016; Wruck and Adjaye, 2020). In addition, in the aging brain and AD, a decrease in the expression of excitatory amino acid transporters 1 (EAAT1/GLAST) and 2 (EAAT2/GLT-1), glutamate transporters expressed mainly by astrocytes, by activated astrocytes is found (Bellaver et al., 2017; Sharma et al., 2019).

The observed imbalance in the glutamate/glutamine ratio in aging astrocytes may also be due to impaired expression of the glutamate synthetase enzyme (GLUL) (Kaiser et al., 2005). Overall, a growing body of evidence suggests an association of astrocyte-mediated excitotoxicity with various neurological disorders, including ALS (Rosenblum and Trotti, 2017), AD (Garcia-Esparcia et al., 2018), PD (Hindeya Gebreyesus and Gebrehiwot Gebremichael, 2020), schizophrenia (Mei et al., 2018), and other neuropathologies (Pajarillo et al., 2019; Todd and Hardingham, 2020).

Another typical molecular feature of senescent brain astrocytes is the increased production of cytokines such as CXCL10/inducible protein-10 (IP-10) (Clarke et al., 2018) and CXCL5, which leads to a chemotactic effect on immune cells (Boisvert et al., 2018). It should be noted that aging cortical astrocytes have a negative effect on the CNS caused by a decrease in the synthesis of some metabolic and trophic factors, such as ATP and neurotrophins (Lalo et al., 2014). A number of studies indicate a decrease in the secretion of neurotrophins in old astrocytes: vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2), and brain-derived neurotrophic factor (BDNF), which undoubtedly leads to a decrease in neuronal survival under stress (Bellaver et al., 2017; Bernal and Peterson, 2011; Verkerke et al., 2021).

Senescent astrocytes accumulate reactive oxygen species and exhibit Ca^{2+} supersaturation (Ishii et al., 2017). Ca^{2+} excess is associated with increased activation of JNK/SAPK kinase, a site of the stress-activated MAPK signaling pathway associated with cell death signaling (Ishii et al., 2017). One of the important signaling Ca^{2+}-dependent pathways involved in astrocyte activation is Ca^{2+}, the calcineurin (CN)/nuclear factor of the activated T-cells (NFAT) pathway (Furman et al., 2012). CN, a calmodulin-dependent protein phosphatase, is a very common calcium-binding protein found in all parts of the brain. Norris et al. showed that CN overexpression in astrocytes contributed to the

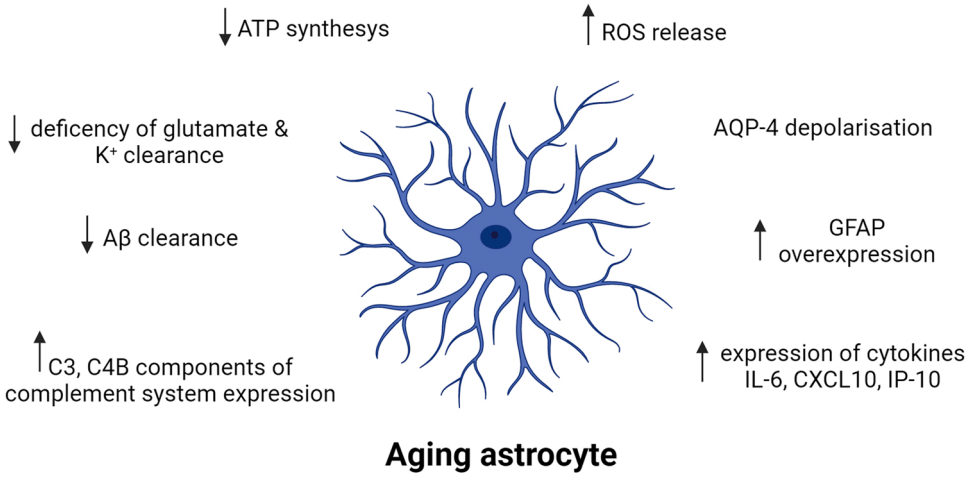

Fig. 4. Metabolic changes in astrocytes as a result of aging. Abbreviations: ATP, adenosine triphosphate. Aβ, amyloid beta. AQP-4, aquaporin-4. ROS, reactive oxygen species. GFAP, glial fibrillary acidic protein. IP-10, inducible protein-10.

development of reactive astrogliosis, which manifested itself in the induction of the expression of genes typical for activated astrocytes (Norris et al., 2005). In astrocytes and microglia, the CN/NFAT pathway is actively activated by many key inflammatory mediators, including cytokines, Aβ, glutamate, and factors associated with vascular injury (Sompol and Norris, 2018). Several studies have found CN activation in pathologies, in particular, AD (Norris et al., 2005; Wu et al., 2010, 2012), PD (Caraveo et al., 2014), and trauma (Furman et al., 2016). Interestingly, several studies have noted that the CN/NFAT pathway links Ca^{2+} dysregulation, neuroinflammation, and impaired glutamate regulation in activated astrocytes, mainly due to reduced EAAT/GLT-1 expression. Also, in astrocytic models of AD, CN inhibition resulted in the activation of GLT-1 expression by astrocytes (Abdul et al., 2009; Sama et al., 2008; Sompol et al., 2017).

It has been noted that reactive astrocytes can also increase the expression of mitochondria-targeted antioxidants. These results suggest that astrocytes are actively involved in counteracting oxidative damage both within themselves and in neighboring cells. However, their molecular mechanisms are insufficient to counteract the oxidative damage that occurs with aging and in age-related neurodegenerative diseases (Licht-Mayer et al., 2015). The genome of senescent astrocytes undergoes pronounced epigenetic changes associated with a decrease in DNA methylation due to a decrease in the synthesis of methyltransferase H3K4 (Chisholm et al., 2015). This can lead to changes in the BBB function by changing the expression of specific transporters and facilitating transport across the BBB (Goodall et al., 2018). Transcriptomic data show that AQP4 and connexin 43 (GJA1) water channel expression is activated with aging in the human frontal, occipital, and temporal cortex, hippocampus, putamen, medulla oblongata, white matter, and cerebellum (Habib et al., 2020; Soreq et al., 2017; Verkerke et al., 2021). Another molecule expressed by astrocytes and playing an important role in the functioning of the BBB is integrin β4 (ITGB4). The expression of β4 integrin in the prefrontal cortex is reported to change with age (Wruck and Adjaye, 2020). The data obtained are in good agreement with other studies and confirm an astrocyte-mediated increase in BBB permeability with age (Farrall and Wardlaw, 2009; Montagne et al., 2015).

Genetic changes in aging astrocytes localized in the suprachiasmatic nucleus (SCN), which play a role in the regulation of circadian rhythms, are of great interest (Brancaccio et al., 2017). Circadian rhythm sleep disorders are a typical manifestation of both normal aging and age-related neurodegenerative diseases (Mattis and Sehgal, 2016). Currently, there is little data on the change in the genetic profile of SCN astrocytes. One of the key molecules that regulate circadian rhythms is Bmal1. Ali et al. reported chronodisruption in *BMAL1*-deficient mice (*Bmal1-/-*) associated with cognitive deficits and progressive brain pathology accompanied by astrogliosis (Ali et al., 2020). Moreover, functional loss of *Bmal1* in mouse astrocytes has been reported to contribute to neuronal death *in vitro*; BMAL1 protein was found to regulate astrocyte activation *in vivo* (Lananna et al., 2018).

One of the key genetic risk factors for sporadic, late-onset AD is the *APOE* gene, or rather its *ε4* isoform *(APOE4)*. ApoE is a glycoprotein involved in the lipid metabolism of the brain. Secreted by astrocytes, ApoE forms a lipoprotein with cholesterol, which binds to neuronal APOE receptors, thereby supporting neuronal function (Zhao et al., 2018). *APOE ε4* carriers show accumulation of ApoE and Aβ plaques, as well as impaired Aβ clearance (Castellano et al., 2011). Carriers of the *ε4* isoform of *APOE* without AD pathology show changes in the expression of complement proteins and other inflammatory markers in the cerebrospinal fluid, including reactive astrocyte markers (CCL4, S100β, YKL40, GFAP), compared with non-carriers of the same age (Konijnenberg et al., 2020). Both aged and *APOE4*-expressing astrocytes exhibit an inflammatory phenotype, indicating that inflammation underlies the increased risk of developing AD, both age-related and associated with the *APOE ε4* genotype.

An epigenetic mechanism for modulating brain functions involving astrocytic ApoE reported by Li et al. (Li et al., 2021a) is of particular interest. Astrocytic ApoE was found to vector a variety of microRNAs (miRNAs) that contribute to the specific silencing of genes involved in neuronal cholesterol biosynthesis, mainly *HMGCS1, HMGCR,* and *CYP51*, ultimately accounting for the substrate acetyl-CoA accumulation. As a consequence, histone acetylation is promoted, and transcription is activated in neurons. ApoE-mediated neuronal histone acetylation results in increased H3K27ac enrichment in the promoters of multiple neuronal immediate-early genes and subsequently enhanced memory consolidation in mice. Deprivation of ApoE reduced histone acetylation levels but also decreased enrichment of specific histone marks, in particular H3K27ac. Human ApoE4s have lower levels of miRNAs than ApoE3s and, as a result, are less capable of metabolic and epigenetic regulation in neurons (Li et al., 2021a).

The construction of predictive models of brain aging based on the analysis of age-related epigenetic changes, including methylome, DNA 5'-methylcytosine (DNAm), is an interesting and promising direction (Li et al., 2021b; López-Otín et al., 2013). In recent work, Trush et al. (Thrush et al., 2022) developed an age predictor algorithm based on epigenetic changes in the brain in AD, linking clinical dementia in AD and *APOE ε4* carrier status. The creation of such algorithms may be useful for studying the heterogeneity of brain aging and epigenetic changes underlying the risk of AD.

There are indications that human astrocytes change with age and upon expression of *APOE4*. Since these glial cells maintain water and ion homeostasis in the brain and regulate neuronal transmission, it is likely that age- and *APOE4*-related changes in astrocytes have a major impact on brain functioning and play a role in age-related diseases (Verkerke et al., 2021).

To sum up, the data accumulated by numerous studies demonstrate significant changes in the genotype of aging astrocytes, which contributes to synaptic loss, the development of neuroinflammation, a decrease in Aβ clearance, and other factors that increase the risk of age-related cognitive impairment and neurodegenerative diseases.

1.1.5.3. The role of astrocytes in age-related neurodegeneration; AD as an example. AD is the most common form of dementia in the elderly population (Arranz and De Strooper, 2019), but aging does not always lead to the development of AD. However, the pathogenesis of AD and aging have common features, including the development of oxidative stress, mitochondrial dysfunction, inflammation, proteotoxicity, and altered gene expression in neurons and astrocytes (Chakrabarti and Mohanakumar, 2016; Sengoku, 2020). It is noted that astroglial changes in neurodegenerative processes are very heterogeneous and regionally specific (Verkhratsky et al., 2019). In animal models of AD, astrocytes undergo degeneration and atrophy in the early stages of pathological progression, leading to early cognitive deficits (Rodríguez-Arellano et al., 2016). In the development of neurodegenerative processes, including AD, it is possible to observe the hypertrophy of astrocytes and their activation. One of the fundamental theories explaining the processes of age-related neurodegeneration is neuroinflammation. The initial inflammatory stimulus (Aβ, pathogenic infection, or cellular debris) triggers microglial activation in the CNS. At the same time, various pro-inflammatory cytokines and chemokines, which direct microglia and astrocytes to the area of inflammation, are released. In a healthy person, this process is well controlled, and immune cells repair the damage, but in AD, the Aβ and tau proteins disrupt the regulation of this mechanism. As a result, microglia and astrocytes cannot effectively clear Aβ, and its overproduction and the lack of effective microglial and astrocytic clearance of the peptide lead to further neurotoxicity and loss of neurons in AD (Minter et al., 2016). Reactive astrocytes are usually found in AD brain tissue in areas with high levels of Aβ or tau protein (Lemoine et al., 2017). Other pathological manifestations of AD, such as microglia activation, can also provoke astrocyte reactivity (Hemonnot et al., 2019; Leng and Edison, 2021; Liddelow et al., 2017). Several major mechanisms for the interaction of astrocytes with Aβ have been

reported. Astrocytes were found to express a wide range of transport proteins and receptors, including the receptor for advanced glycation end products (RAGE), lipoprotein receptor-related proteins (LRPs), scavenger receptor class B member 1 (SCARB1), and proteoglycans that bind to Aβ (Batarseh et al., 2016; Fakhoury, 2018). The LRP1 molecule is efficient in the uptake of Aβ monomers but not Aβ oligomers (Li et al., 2014). In turn, SCARB1 interacts with fibrillar Aβ (Husemann et al., 2001), and RAGE is able to interact with three forms of Aβ (Batarseh et al., 2016; Mohamed and Posse de Chaves, 2011).

It is important to note that astroglia atrophy occurred in various regions of the brain before the appearance of extracellular Aβ deposition. The morphological atrophy of astroglial cells reflects a decrease in their contacts with synaptic endings. Astroglial atrophy may be directly related to a decrease in astroglial homeostatic support, which can have severe consequences for neuronal survival and the functional activity of synapses (Rodríguez-Arellano et al., 2016).

Interestingly, some studies have suggested that depolarization of astrocytic AQP4 is an important factor in impairing Aβ glymphatic clearance, thereby increasing the probability of its aggregation, which may play an important role in the course of AD (Tarasoff-Conway et al., 2015; Xuan et al., 2022; Zeppenfeld et al., 2017). On the other hand, there are a number of studies noting that AQP4 depolarization is driven by the formation of insoluble Aβ aggregates. This may contribute to the structural activation of astrocytes around Aβ plaques, thereby protecting neurons from the harmful effects of Aβ aggregates (Hoshi et al., 2012; Silva et al., 2021; Smith et al., 2019). To date, the nature of the relationship between AQP4 and AD remains controversial, and the question remains whether loss and depolarization of astrocytic AQP4 is a consequence or cause of Aβ accumulation.

In fact, reactive astrocytes contribute to neuroinflammatory changes in AD by releasing cytokines, inflammatory factors, nitric oxide, and reactive oxygen species, and by contributing to the disruption of redox status (Fig. 5). It has been shown that neurons in AD increase insulin-like growth factor 1 (IGF-1) expression by interacting with astrocytes, which can lead to increased formation of amyloid-beta by neurons (Costantini et al., 2010). In turn, Aβ can stimulate astrocytes and cause activation of the NF-κB pathways (which is considered an important factor in the development of neuroinflammation in AD) (Kumar and Kumar, 2019; Shi et al., 2016; Wang et al., 2013). Consequently, the production of pro-inflammatory cytokines such as IL-1β, IL- 6, iNOS, and TNF-α increases (Bales et al., 1998; Geng et al., 2019).

As is known, changes in the calcium concentration can be a trigger for starting the transcription of molecules and activating cell signaling systems. The CN/NFAT signaling pathway is one of the most interesting in the context of the cellular response of astrocytes in AD. As discussed in the previous section, calcineurin activation is an important factor in altering astrocyte activity in AD. The addition of oligomeric Aβ to primary cultures of rat astrocytes strongly stimulated NFAT activation (Abdul et al., 2009). Moreover, in mice with a 5xFAD model of AD, an increase in the expression of GLT-1 by astrocytes was shown, as well as the absence of morphological disorders of neurons after the inhibition of CN/ NFAT pathways using VIVIT (Sompol et al., 2017).

Dysregulation of Ca^{2+} ion transfer is widely considered an important component of neurodegenerative diseases, including AD (Verkhratsky et al., 2017). The increase in the Ca^{2+} concentration in neurons within the depolarization phase, as well as at rest, observed during aging is called the "calcium hypothesis of aging". An acute disturbance of Ca^{2+} homeostasis and Ca^{2+} signaling in the presence of Aβ is observed. Treatment with Aβ (at concentrations from 100 nM to 5 μM) for several hours increased [Ca^{2+}] at rest by two to three times compared with the

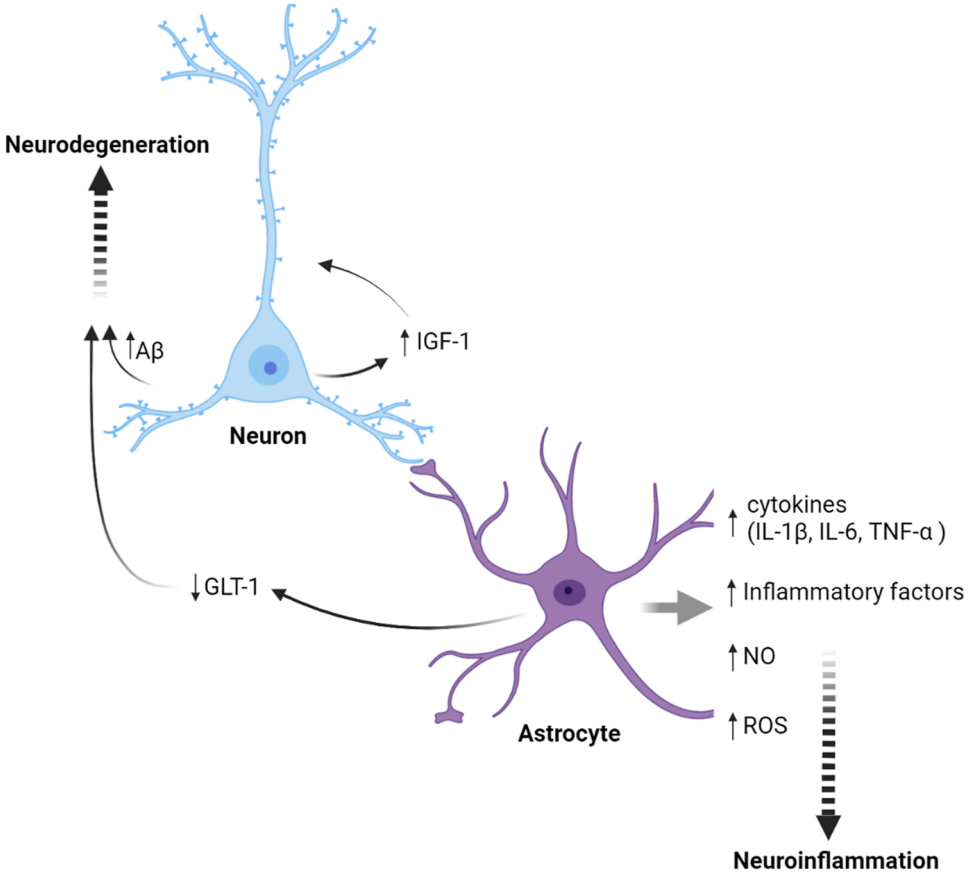

Fig. 5. Astrocyte-mediated association of neuroinflammation and neurodegeneration in AD. Abbreviations: Aβ, amyloid beta. IGF-1, insulin-like growth factor 1 receptor. GLT-1, glutamate transporter type 1. IL-1β, interleukin 1 beta. IL-6, interleukin 6. TNF-α, tumour necrosis factor α. NO, nitric oxide. ROS, reactive oxygen species.

initial levels (Verkhratsky, 2019). Changes in calcium signaling were observed in astrocytes obtained from various transgenic *in vivo* models of AD. A sufficiently strong (two-fold) increase in $[Ca^{2+}]i$ at rest, as well as aberrant $[Ca^{2+}]_i$ activity associated with the generation of abnormal long Ca^{2+} waves, was found in astrocytes associated with senile plaques in APP/PS1 mice. Contact of astrocytes with Aβ triggers $[Ca^{2+}]_i$ oscillations resulting from the IP_3-mediated release of Ca^{2+} from the ER; pharmacological suppression of these oscillations inhibited both $[Ca^{2+}]_i$ dynamics and astroglial reactivity. In other experiments, astrocytes showed a higher frequency of spontaneous fluctuations in calcium even before the appearance of amyloid plaques. (Verkhratsky et al., 2017). The onset of $[Ca^{2+}]_i$ hyperactivity is said to be associated with abnormal purinergic signaling in reactive astroglia cells. It is assumed that reactive astrocytes secrete excessive amounts of ATP through connexin hemichannels. This ATP, in turn, has an autocrine effect on the P2Y purinoceptors of astroglia, which mediate changes in Ca^{2+} dynamics (Verkhratsky, 2019).

Interestingly, recent experiments have shown that astrocytic α2-Na^+/K^+ adenosine triphosphatase (α2-NKA) is elevated in post-mortem human brain tissues from AD and a mouse model of tauopathy. Pharmacological inhibition of α2-NKA suppresses neuroinflammation and reduces brain atrophy by regulating the pro-inflammatory protein lipocalin-2 (Lcn2) (Mann et al., 2022).

In experiments on transgenic mouse models of AD (Oddo et al., 2003; Yeh et al., 2011), early morphological atrophy of astroglial cells preceded the appearance of Aβ deposits and senile plaques (Beauquis et al., 2013; Yeh et al., 2011). Using 5XFAD Alzheimer mouse model, a recent study detected a population of disease-associated astrocytes in the early stages of the disease. Their number increased as the disease progressed (Habib et al., 2020). On the other hand, a recent study by Lee et al. demonstrated early intracellular accumulation of Aβ by neurons in *in vivo* mouse models long before extracellular plaque formation (Lee et al., 2022). The impairment of neuronal autophagy due to lysosomal dysfunction, often observed in AD, was accompanied by intracellular deposition of Aβ packaged in autophagic vesicles forming flower-like perinuclear rosettes, also known as PANTHOS. In model mice 5xFAD/TRGL with early onset of AD, by 2.2 months of development, about 50% of neurons with a PANTHOS profile were thioflavin-S positive, indicating accumulation of Aβ by these cells. It is noteworthy that immunochemical labeling of GFAP and IbaI did not reveal a connection between PANTHOS neurons and astrocytes/microglia at the early stages (2.7 months), which excluded the contribution of these cells to the development of PANTHOS and further formation of senile plaques (Lee et al., 2022).

Moreover, Hefendehl et al. found abnormalities in glutamatergic astrocyte homeostasis in AD. Decreased levels of the GLT-1 in the microenvironment surrounding the Aβ plaque were observed in mouse models of AD (Hefendehl et al., 2016; Peterson and Binder, 2019). A recent report by Du et al. demonstrated the neuroprotective effect of astrocytic GluN2A receptors. Astrocyte-specific knockdown of Grin2a (the gene encoding GluN2A) in the rat hippocampus counteracted the Aβ-induced compensatory protective increase in β-NGF by modulating pNF-κB, Furin, and VAMP3, which affect the synthesis, maturation, and secretion of NGF (nerve growth factor), respectively. This *in vivo* study has shown a new neuroprotective mechanism mediated by astrocytic GluN2A, which actively affects synapses at an early stage of exposure to Aβ oligomers (Du et al., 2021).

Summing up, recent findings point to a significant role of astrocytes in the progression of neurodegenerations, in particular, in AD. Over the last decades, treatment of this complex disease has focused on correcting cellular metabolism to prevent neuronal damage (Duran et al., 2019; Magi et al., 2021; Wu et al., 2022). However, this approach has not brought significant results, and AD remains the scourge of an aging population. The focus should now be placed on correcting the metabolism of cells that control the activity of neurons and influence the processes in the brain. It is important to note the possibility of considering astrocytes as a sex-specific therapeutic target for pathologies of the nervous system, as well as aging-related brain damage.

1.2. The functions of astrocytes in sleep & sleep disorders

It is believed that behavioral, physiological, and electrocortical sleep/wake states are governed by complex interactions between subcortical neuromodulatory neurons located in the brainstem, midbrain, hypothalamus, basal forebrain, thalamus, and cerebral cortex (Arrigoni et al., 2016; Luppi et al., 2017). However, in addition to the neuronal regulation of sleep, the role of astrocytes in this process has recently gained interest since the role of these cells in synaptic transmission has become evident (Halassa et al., 2007; Noriega-Prieto and Araque, 2021; Santello et al., 2012).

The concept of the role of astroglia in sleep regulation was introduced more than a century ago by Santiago Ramón y Cajal, who suggested that by penetrating the synaptic cleft, astroglial processes could slow down communication in neural networks and thereby induce sleep (y Cajal, 1921). Carl Ludwig Schleich (Schleich, 1894) also considered a very similar mechanism as the basis for general anesthesia. Among modern studies, it is worth mentioning the work of Pelluru et al., which used optogenetic methods to demonstrate a clear role of astrocytes in sleep modulation (Pelluru et al., 2016). A transgenic mouse model selectively expressing the dominant-negative (dn)-SNARE domain in astrocytes is one of the most widely used models for studying the role of astrocytic gliotransmission in the regulation of sleep/wakefulness (Deng et al., 2011; Halassa et al., 2009; Schmitt et al., 2012).

To date, there are two main known mechanisms that regulate the sleep/wake cycle: circadian rhythm and homeostasis.

1.2.1. Astrocytic modulation of sleep homeostasis

Several gliotransmitters are known to affect sleep/wake cycles in animals, including humans. In particular, some experiments have demonstrated the modulation of sleep homeostasis by ATP-mediated formation of adenosine (Greene et al., 2017; Holst and Landolt, 2015; Porkka-Heiskanen and Kalinchuk, 2011). Interestingly, astrocytic processes approach the synaptic cleft during wakefulness and provide greater coverage than during sleep (Bellesi et al., 2015). The authors attributed this process to the increased need for glutamate clearance during wakefulness (Wigren and Porkka-Heiskanen, 2018).

More than a century ago, it was discovered that the cerebrospinal fluid of sleep-deprived animals contains substances that could promote sleep in other animals (Ishimori, 1909; Legendre, 1913). This discovery led to the hypothesis that wake-dependent homeostatic substances accumulate when awake, and once a certain concentration is reached, they are recognized by the homeostatic system, which facilitates the sleep process. The main homeostatic substances and regulation mechanisms include adenosine and its receptors A1 and A2A, cytokines such as interleukin-1, tumor necrosis factor α and prostaglandin D2, and nitric oxide (Brown et al., 2012; Mang and Franken, 2015; Morairty et al., 2013). In particular, early studies showed that the cytokine IL-1, obtained from cultured mouse astrocytes, increases NREM sleep in rats when injected into the ventricles (Tobler et al., 1984).

Astrocytes are believed to play a key role in the homeostatic regulation of sleep/wake processes by releasing ATP into the extracellular space. It is then converted into adenosine, the most important regulator of sleep homeostasis (Pascual et al., 2005). By binding to the pre- and postsynaptic neuronal receptors A1 and A2A, adenosine promotes the regulation of synaptic transmissions (Blutstein and Haydon, 2013; Fellin et al., 2012; Halassa et al., 2009; Haydon, 2017). Table 2 (see Supplementary) summarizes the studies results demonstrating astrocytes involvement in sleep process regulation. In the recent study by Hablitz et al., it was suggested that neuronal activity generates endocannabinoid release by activating astrocyte Ca^{2+} signaling that releases adenosine and activates adenosine-1 receptors (A1R) on presynaptic terminals, decreasing GABA release (Hablitz et al., 2020).

Also, ANLS functioning is closely related to the sleep/wake cycle. The release of lactate from astrocytes is thought to be associated with glutamatergic (excitatory) synaptic activity. A significant increase in the mRNA levels of genes involved in ANLS functioning (*Glut1*, α-2-Na/K pump, *Glt1*, and *Ldha*) was found in astrocytes following sleep deprivation in mice (Petit et al., 2013).

More recent studies show that astrocytes play an important role in "cleaning the brain" during sleep. Iliff et al. are the first to report the existence of the GS in the CNS, which is an alternative clearance system located in the perivascular space and is dependent on astrocytic AQP4. It was shown that the glymphatic pathway, which is highly dependent on astrocytic aquaporin, is capable of removing solutes from the brain and that a defect in this pathway may contribute to the development of AD (Haydon, 2017; Iliff et al., 2012). Glymphatic clearance is most effective during sleep, and sleep disturbances are closely associated with the development of neurodegenerative diseases (Augusto-Oliveira and Verkhratsky, 2021). Sleep deprivation was found to be accompanied by increased levels of intracerebral tau and ß-amyloid (Holth et al., 2019; Shokri-Kojori et al., 2018). Natural sleep or anesthesia is associated with a 60% increase in the interstitial space, resulting in a significant increase in convective exchange of cerebrospinal fluid with interstitial fluid and a consequent increase in the rate of Aβ clearance during sleep (Xie et al., 2013). Gordleeva et al. proposed a causal relationship between cellular aging processes, impaired brain clearance due to GS and BBB dysfunction, induction of glial inflammation, and sleep disturbances with the help of mathematical modeling. Accepting the hypothesis that lack of sleep leads to an increase in the concentration of by-products of neuronal activity and contributes to aging, the model predicted that when the accumulation of senescent glia exceeds a certain inflammation threshold, further aging progression becomes unstoppable, even when the sleep process is normalized. This process can be reversed only by reducing the concentration of senescent glia below this threshold value (Gordleeva et al., 2020). More recent data from human studies and rodent models indicate that GS is critical for maintaining brain health and that GS dysfunction is strongly associated with various neurological disorders, aging, neurodegenerative diseases, and acute brain damage, including ischemia (Lv et al., 2021; Ren et al., 2021; Xia et al., 2017). The role of astroglia in altering the sleep process in psychiatric disorders is also a point of great interest. A possible contribution of astrocyte atrophy and asthenia observed in patients with bipolar disorder to changes in the sleep profile has been reported. This observation may be of great interest for using astrocytes as further therapeutic targets for this disorder (Steardo et al., 2019).

1.2.2. *Circadian regulation of sleep by astrocytes*

In all species studied, brain astrocytes contain a conserved circadian clock, and numerous studies have shown that these glial cells are involved in the regulation of circadian behavior and sleep (Jackson et al., 2015, 2020).

The circadian system of sleep/wake regulation in mammals is coordinated by a central pacemaker located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus (Saper and Scammell, 2013). It has been experimentally proven that SCN damage leads to circadian rhythm disturbance in sleep/wake states and, consequently, to sleep fragmentation; this also occurs in nonhuman primates (Edgar et al., 1993).

Astrocytes in SCN exhibit rhythmic oscillations of intracellular Ca^{2+} (Van den Pol et al., 1992) *in vitro* and undergo structural and molecular changes in astrocytic connections with synapses (Lavialle et al., 2011). It is believed that the calcium activity of neurons and astrocytes in SCN alternates. The peak of neuronal activity occurs during the circadian light phase, and the activity of astrocytes during the dark phase of the circadian cycle (Brancaccio et al., 2017). Using bioluminescence, it was demonstrated that SCN astrocytes in organotypic cultured slices and dissociated cell cultures exhibit circadian fluctuations in the expression of the "clock genes" responsible for circadian rhythms (*Clock, BMAL1, PER1,* and *Per2* and *Cry1*) independently of neurons (Brancaccio et al., 2019; Welsh et al., 2010). Astrocytic *Per2* expression leads to circadian fluctuations in glutamate synthesis and reuptake, regulating network-wide excitability by decreasing glutamate levels during the dark phase (Chi-Castañeda and Ortega, 2018; Leone et al., 2015). Some data indicate that astrocytes can directly influence the rhythmicity of SCN neurons (Brancaccio et al., 2017; Broadhead and Miles, 2021; Clasadonte et al., 2017; Prosser et al., 1994).

Molecular analysis of astrocytes also showed that a number of genes involved in the elongation of astrocytic processes surrounding synapses are activated during wakefulness (Bellesi et al., 2015). In addition, the levels of mRNA and protein Fabp7, a mammalian brain fatty acid-binding protein involved in astrocyte plasticity, were shown to be synchronized with the sleep-wake cycle in rodents (Gerstner et al., 2012); mutations in the *FABP7* gene reduced sleep duration in flies, humans, and mice (Gerstner et al., 2017).

It is important to note that attenuation of astrocytic 1,4,5-trisphosphate (IP_3) and Ca^{2+} signaling leads to modulation of REM sleep and theta rhythm power (5–8 Hz). When interastrocytic Ca^{2+} signaling was impaired in mice, they spent more time in the REM phase (Foley et al., 2017). Several other studies have also confirmed the importance of astrocyte Ca^{2+} signaling and the integrity of the astrocyte network for normal function, as well as for regulation of the sleep process (Bojarskaite et al., 2020; Clasadonte et al., 2017; Ingiosi et al., 2020).

Thus, gaining more detailed knowledge of the pathologies of the nervous system requires a clearer understanding of the mechanisms underlying the connection between circadian rhythms and homeostatic regulation of sleep/wake processes at the cellular and molecular levels.

2. Conclusions

It has become well known that astrocytes, in addition to their classical trophic function, play an important role in complex processes such as sleep, information processing, aging, and the development of various pathological conditions, including neurodegenerative diseases. Though they are not electrically excitable, astrocytes can generate Ca^{2+} waves in response to neuronal activity. It is assumed that the slower transmission of astrocyte Ca^{2+} signals in comparison with neuronal Ca^{2+} signals contribute to the synchronization of brain activity.

Many findings confirm the important functional role of astrocytes in age-related brain changes, including sleep disturbance and the development of neurodegenerative diseases (see Supplementary, Table 3). Among the most striking examples of such regulation are adenosine-dependent regulation of sleep homeostasis (Dworak et al., 2010), changes in the sleep pattern upon disconnection of interastrocytic signaling in model animals (Bojarskaite et al., 2020; Clasadonte et al., 2017), sleep/wake cycle disorders in mice with impaired gliotransmission (Halassa et al., 2009; Schmitt et al., 2012). Other examples are presented in this review or shown in Table 2 (see Supplementary).

Astrocytes play a special role in the neuroinflammation processes; this function of astrocytes can be considered an important factor of brain aging and the development of many neurodegenerative diseases. All of these results make it clear that astrocytes are important players in the development of neurodegenerative diseases, as well as brain aging. Sleep disturbances observed in age-related neurodegenerative diseases, the involvement of astrocytes in tau and ß-amyloid clearance, as well as significant changes in astrocytes associated with an increase in intracellular calcium and activation of the inflammatory phenotype, not only open up the possibility of studying the role of astrocytes in pathological sleep disturbances in neurodegenerative diseases but also make astrocytes a promising therapeutic target. Nevertheless, the question of whether sleep disturbances are a direct consequence of age-related changes in the nervous system, an early manifestation of pathologies and/or whether they contribute to the neurodegenerative process is open and requires further and more detailed study.

For a long time, neurons were classically considered the main objects for studying brain pathologies, including neurodegenerative diseases.

BOX: Sex differences in sleep

Sex is an important factor in sleep change (Luca et al., 2015). Insomnia is more common in women than men for most of their lives. The ratio of insomnia in women to men is approximately 1.4:1.0; however, the difference is minimal before puberty and steadily increases with age (Phillips et al., 2008). Typically, women complain about difficulty falling asleep (Rodin et al., 1988), while men are more likely to have trouble maintaining sleep, lighter sleep, and more frequent sleep-related breathing disturbances (Wilhoit and Suratt, 1987). More recent studies also revealed sex differences in sleep EEG. Differences between men and women in terms of brain maturation, perceived sleep, NREM-REM distribution, or EEG characteristics were suggested (Armitage, 1995; Dijk et al., 2010, 1989). The prevalence of obstructive sleep apnea syndrome also increases with age (Tufik et al., 2010). Periodic limb movements during sleep (often associated with restless legs syndrome) are common in the general population and increase with age in both men and women (Moraes et al., 2014). Besides sleep disturbances, dementia is also one of older people's most common and serious health problems. A growing body of research shows that sleep disorders can influence the pathogenesis of dementia of all causes or their subtypes, including AD and vascular dementia (Jee et al., 2020).

Nevertheless, the results of numerous studies demonstrated the key role of astrocytes in the development of nervous system pathologies. Undoubtedly, astrocytes can be considered an object for the search for new therapeutic targets for age-related neurodegenerative diseases. However, more in-depth studies are needed on how astrocytes interact with other cells of the nervous system, in particular, a more extensive understanding of the interaction of astroglial networks with microglia and neurons. However, it is practically impossible to conduct studies of neuron-glial interactions and astrocytic networks in the brain. Therefore, there are currently numerous experimental models in neuroscience. Mini brain organoid technology has evolved from promising approaches that could provide new insights into the role of astrocytes in the development of neurodegenerative processes and open the prospects for effective therapeutic interventions. This technology involves the collection of induced pluripotent stem cells (iPSCs). A key advantage of cell reproduction is the ability to obtain PSCs from patients with certain genetic variations that may contribute to disease. The flexibility of organoid coculture approaches can also be helpful in studying neuroinflammatory and neurovascular processes, as well as interactions with other areas of the brain. Thus, the use of mini brain organoids is a promising new biomedical approach for drug testing, as well as improving cognitive health and lifespan. Using the application to study the patterns of reorganization of astroglial networks during normal and pathological changes in the CNS is promising and certainly of interest for neurobiology.

CRediT authorship contribution statement

Sergey V. Gudkov, Claudio Franceschi and Maria V. Vedunova conceived the paper, Dmitriy E. Burmistrov, Sergey V. Gudkov and Elena V. Kondakova wrote the original manuscript, Dmitriy E. Burmistrov drew all the figures, Dmitriy E. Burmistrov and Elena V. Kondakova collected the data in the table, Ruslan M. Sarimov, Roman S. Yarkov and Claudio Franceschi revised the manuscript, Sergey V. Gudkov, Dmitriy E. Burmistrov, Elena V. Kondakova, and Maria V. Vedunova checked all the references and manuscript. All authors approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2022.101775.

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