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Review Article

Reactive Astrogliosis and Neuronal Functions of Astrocytes in Neurological Disorders

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ABSTRACT

Astrocytes are the most abundant cells in the brain. Astrocytes take part in the absorption and recycling of neurotransmitters, inflammation, neuroenergetics, the release of gliotransmitters, the regulation of synaptic activity, the maintenance of the blood-brain barrier, and other processes. Astrocytes help to keep the central nervous system healthy and functioning properly. These cells are linked to the onset and progression of various neurodegenerative diseases. Recent research has revealed that these cells play a variety of active roles in both normal physiological homeostasis in the brain and neurodegeneration and disease. Astrocytes play a role in nervous system functions and the pathogenesis of Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. This review sheds light on the role of astrocytes in neuronal function and their mechanisms in synaptic transmission. We also summarized astrocytes' roles in various neurological diseases.

Keywords: Astrocytes, Alzheimer's disease, Multiple sclerosis, Neurodegeneration, Parkinson's disease.

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INTRODUCTION

Astrocytes are the most common type of cell in the central nervous system. Astrocytes are important in synaptic transmission and information processing through neural circuit functions. Astrocytes also influence neural precursors in the adult Central Nervous System (CNS).[1,2] These cells maintain CNS homeostasis by synthesizing glycogen and supplying energy substrates to neurons. Astrocytes have an electrically non-excitable membrane potential (Vm) of around -80 mV at rest. Gap junctions are the specialized sections of adjacent cell membranes punctured by hundreds of intercellular channels that integrate astrocytes into the cellular networks (syncytia) of the CNS. Astroglial syncytia are separated physically within various anatomical regions of the mammalian CNS. Astroglial syncytia lives in individual barrels in the sensory cortex and individual glomeruli in the olfactory bulb.[3,4] Carl Ludwig proposed that the astrocytes are involved in controlling information flow in the brain. The astroglial process regulates synaptic transmission through swelling and shrinking. Cajal proposed the role of astrocytes in the brain vasculature and the facilitation of functional hyperemia. The astroglial perivascular process regulates blood flow by increasing or decreasing the diameter of brain capillaries. Figure 1 represents various functions of astrocytes in the healthy CNS.

Physiology of Astrocytes

Astrocytes are excitable cells and communication elements that do not create action potentials. In gliotransmission, astrocytes are activated by internal or external impulses and deliver specialized messages to neighbouring cells.[6] Astrocytes are the main element of the homeostatic system and control all aspects of metabolic support, nutrition, ion control, neurotransmitter atmosphere, Blood Brain Barrier (BBB) regulation, and CNS defense.[7] Astrocytes have a diverse set of signaling pathways and trans-cellular communication via gap junctions. Astrocytes release gliotransmitters via multiple regulated pathways. This complex signaling mechanism may include astrocytes in information processing procedures in the CNS. This makes astrocytes an essential component in creating higher cognitive capabilities in the brain.

The human brain has various types of astrocytes, one of which is protoplasmic astrocytes. These astrocytes are predominantly found in the grey matter of the brain and spinal cord (Figure 2a). Fibrous astrocytes are present in the cerebral cortex and white matter of the spinal cord, as well as in the optic nerve and retinal

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nerve fiber layer (Figure 2b). The presence of surface-associated astrocytes is observed in some regions of the brain, including the posterior prefrontal and amygdaloid cortex. These astrocytes are characterized by their connection to the cortical surface.[8] Velate astrocytes are a type of astrocyte that can be found in the brain. The astrocytes in the arcuate nucleus of the hypothalamus, which contain a significant amount of iron, exhibit positive staining when subjected to Gomori's chrome-alum hematoxylin staining technique. Perivascular astrocytes are located in close proximity to the pia mater, where they form many endfeet that surround blood vessels.[9]

Physiology of Astrocyte Membrane

The concentrations of cytosolic and extracellular ions differ in astrocytes from those in other living cells. Cytosolic ion concentration is related to membrane permeability and energy-dependent active transport. A high concentration of Cl- ions (30 mM-60 mM) is assumed in astrocytes. The most distinctive electrophysiological feature of adult astrocytes is their hyperpolarized resting potential (about 80 mV) and low input resistance (520 M). These electrophysiological features indicate strong resting membrane permeability for K^+. Despite their physical differences, astrocytes exhibit electrophysiological properties similar to hyperpolarized membrane potential and a preference for passive K^+ permeability.[11,12] The electrodriving force for multiple membrane transporters is defined by the negative and steady potential of astrocytes in their resting state. This determines their homeostatic capacities.

Receptors in Astrocytes

Astrocytes can express nearly every receptor identified in the CNS, allowing them to observe the neurochemical landscape of nerve tissue.[13] Gamma-Aminobutyric Acid (GABA) or Acetylcholine (ACh) iontophoretic injections cause depolarization of glial cells. This could be due to the regulation of the membrane ion pump. The functional expression of glutamate, glycine receptors, and GABA has been established in direct electrophysiological recordings from cultured astrocytes free of neuronal contamination. Several receptors, such as glutamate, purinoreceptors, GABA, glycine, adenosine, muscarinic, adrenergic, serotonin, histamine, etc. have been reported.[14,15] The neurotransmitter receptor modalities expressed by astroglia are similar to those expressed by their neuronal neighbours and are most likely influenced by the local neurotransmitter environment.[16,17]

Association of Astrocytes with Ion Channels

K^+ release-related depolarization can be used by astrocytes to detect neuronal activation. Gap junctions connect astrocytes to nearby astrocytes, allowing ions and tiny molecules to flow between them.[18,19] Adenosine Triphosphate (ATP) binding to the P2X7 receptor is largely responsible for Ca^{2+} waves. By initiating the release of nutrients and controlling blood flow, these Ca^{2+} waves control neighbouring neuronal activity.[20,21] Depending on the specificity of the brain area, subtypes of astrocytes such as protoplasmic and fibrous astrocytes, ependymal glia, bergmann glia, marginal glia, radial glia, perivascular glia, and tanycytes have been reported in adult mice.[8] Human astrocytes are more complex than rodent astrocytes. Human astrocytes, viz., glial fibrillary acidic proteins, are larger and more complicated than their rodent counterparts. Human astrocytes have superior Ca^{2+} responses, a higher Ca^{2+} velocity wave, and more connections with the surrounding cells.[9] In the human cortex, the astrocyte-to-neuron ratio is 1.65, while in rodents it is 0.35. The brain becomes more complex and larger if it has a higher astrocyte-to-neuron ratio.[22,23]

Voltage Gated Ca^{2+} Signal Role of Astrocytes

In the cell membrane, astrocyte Ca^{2+} channels can be responsible for intracellular Ca^{2+} influx. Voltage Gated Calcium Channel (VGCC) is composed of 1-subunits that interact with modulatory accessory subunits (different β- and α 2δ-subunit isoforms) to form a hetero-oligomeric complex.[24,25] Separate genes encode 10 α1-subunits with different properties, and different expressions throughout the tissues have been reported. VGCC has two main groups: (i) high-voltage-operated Ca^{2+} channels, and (ii) low-voltage-activated channels.[26-28] Throughout the brain, astrocytes enclose tiny arterioles and capillaries to generate connections between the terminals of astrocyte processes and the basal lamina that surrounds endothelial cells. Astrocyte hypertrophy is characterized by enlargement of astrocyte size and variations in morphology. It commonly occurs in neuroinflammatory illnesses.[29,30]

Active synapses release glutamate, which can attach to astrocyte G protein-coupled receptors. High extracellular K^+ causes

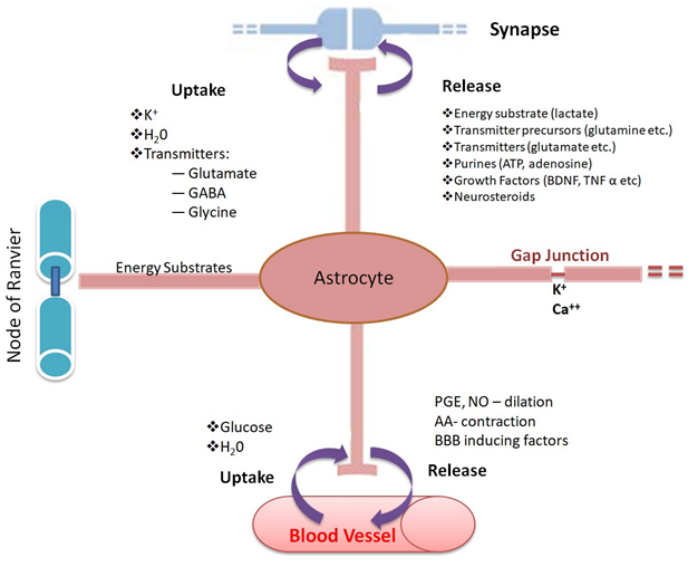

Figure 1: Representation of astrocytes functions in healthy CNS. Re-drawn with permission from Sofroniew and Vinters.[5] Copyright© 2009, The Author(s) and Springer Nature.

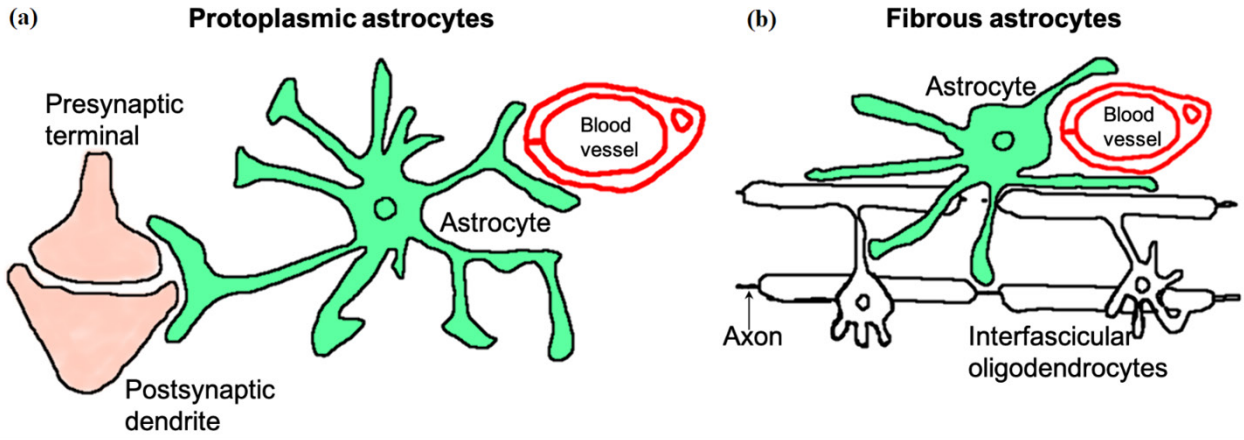

Figure 2: Fibrous and protoplasmic astrocytes in the central nervous system: (a) contact of fibrous astrocytes with blood veins and axons in the white matter (b) contact of protoplasmic astrocytes with blood veins and synapses in the gray matter. Re-drawn with permission from Kim *et al.*[10] Copyright© 2019, The Author(s) and MDPI.

depolarization of astrocytes, resulting in an increase in the frequency of Ca^{2+} events via VGCC activation in cultured astrocytes. Reactive astrocytes release inflammatory cytokines, viz., Tumor Necrosis Factor alpha (TNFα) and Prostaglandin E2 (PGE2 through activated B cell's kappa-light-chain-enhancer) (NF-κB) signaling.[31,32] During CNS injury, astrocytes stimulate TNFα, PGE2, ATP, glutamate, and D-serine release, in addition to intense cytosolic Ca^{2+} waves.[33]

Role of Big Conductance K^+ (BK) Channels in Astrocytes

Presynaptic astrocytes control the K^+ ion's homeostasis and the regulation of extracellular Ca^{2+}. VGCCs are spatially close to BK channels and have direct physical interactions with them. BK channels become activated at a membrane potential of zero mV at ≥10 μM Ca^{2+} concentration.[34] In both excitable and non-excitable cells, BK and Ca^{2+} channels can form complexes to reduce energy expenditure and fine-tune Ca^{2+} regulation.[35] In the mouse brain, dilation and constriction of arterioles through BK channels depend upon astrocytic endfoot Ca^{2+} levels.[36] A moderate increase in this level causes dilation (300-400 nm); a large increase (>700 nM) causes constriction. K^+ releases into the perivascular space due to the activation of astrocytic BK channels by astrocytic end foot Ca^{2+}.[37] Extracellular K^+ ions are required for rapid dilation and constriction. In the rat brain, co-expression of BK channels with Aquaporin-4 (AQP4) water channels affects BK channels in the redistribution of K^+ and cerebral blood flow regulation.[38] Thus, the tone of cerebral vessels and flow of blood are influenced by BK channel activation in astrocytes mediated by calcium.

Ion Channel Homeostasis in Neurodegeneration

The optimal operation of these entities is crucial for the preservation of the intricate equilibrium of ions and the facilitation of effective transmission of electrical impulses. Neurodegeneration has been linked to ion channel dysregulation, highlighting the need to understand their complex role in disease development. Understanding ion channel homeostasis can lead to new neurodegenerative disease treatments and better lifestyles for those affected. Ion channel homeostasis defects can result from genetic mutations, environmental conditions, or aging.[39] Disrupted ion channel balance can cause excessive or inadequate ion flow, altering electrical impulses and neuron communication. This disturbance causes neuronal malfunction, oxidative stress, inflammation, and degeneration. Decoding neurodegenerative pathways requires understanding ion channel homeostasis.[40] Targeting ion channels and their regulatory processes may allow novel therapies to restore balance and delay neurodegenerative disease development. Ion channels allow sodium, potassium, calcium, and chloride to flow in and out of neurons via specialized proteins on the cell membrane. The precise equilibrium of ion mobility plays a pivotal role in the optimal operation of neurons, as it governs a range of cellular mechanisms, such as electrical signaling and synaptic transmission. However, dysregulated ion channels can harm neurons and cause neurodegenerative disorders. Abnormalities in ion channel homeostasis have been observed in AD, Parkinson's disease (PD), Huntington's disease, and amyotrophic lateral sclerosis.[41] Disrupted calcium homeostasis in AD can impair neuronal transmission and cause amyloid plaques and neurofibrillary tangles. Mutations in ion channel genes cause dopaminergic neurons to malfunction in Parkinson's disease, causing movement symptoms. The mechanisms of ion channel deregulation in neurodegenerative disorders are complex and require multidisciplinary research.[42] The complicated relationships between ion channel homeostasis and neurodegeneration will hopefully help scientists find new therapeutic targets and develop techniques that reduce the progression of these fatal conditions.

Astrocytes Contribution in Neuronal Functions

Along with regulating blood flow, astrocytes are involved in mitochondrial transmission to neurons and provide the

building blocks for neurotransmitters, which are used to power neuronal metabolism.[43-45] Moreover, astrocytes are involved in phagocytosing synapses, altering neurotropin secretion, and clearing debris.[46,47] Throughout development, astrocytes and neuronal crosstalk appear to begin, gliogenesis and synaptogenesis occur concurrently in the brain, and glial cell development signals the end of the synaptogenic and neuroplastic phases.[48] In addition to astrocytic neuron cooperation, the astrocytic process overlaps with the nearby astrocytes.[49] When these astrocytes establish gap junctions, the functional network forms, resulting in highly ordered anatomical regions.[50] Concerning the CNS injury, astrocytes become reactive. The reactive astrocytes have heterogeneity, which divides them into two classes (A1 and A2 reactive astrocytes) and results in gene expression alteration, cell hypertrophy, and glial scar formation.[51] NF-κB pathway that controls A1 astrocytes also affects the neurovascular component.[52] On the other hand, the scar-producing astrocytes (A2-reactive) enclose the damaged BBB through glial scar formation.

A1-type astrocytes express more genes that are harmful to synapses during neuroinflammation. A2-type astrocytes enhance the production of genes that are helpful to the growth and survival of neurons during ischemia. Activated microglia cause A1-type astrocytes to grow by raising the levels of Interleukin-1 (IL-1), TNFα, and C1q. The number of A1 astrocytes is increased in Alzheimer's disease (AD) and other neurodegenerative diseases. In neuro-inflammatory conditions, A1 astrocytes fail to promote astrocyte-neuron connections and become neurotoxic.[53] Neurotransmitters like ATP, glutamate, and D-serine are upregulated and released by astrocytes, influencing paracrine transmission among neurons, astrocytes, pericytes, microglia, and endothelial cells.[54] Under physiologic conditions, interference between neurons and astrocytes plays an important role. It disrupts the interference between astrocytes, neurons, microglia, and endothelial cells, resulting in impaired neurodegeneration.[55,56]

Mechanism of Synapse Formation and Elimination by Astrocytes

Interactions between neurons and glia actively control brain homeostasis via correct synaptic plasticity and neurotransmission release. The tripartite synapse is related to the respective network of cells, including presynaptic neurons, postsynaptic neurons, and astrocytes.[57] Astrocytes are responsible for the formation of synapses by constructing tripartite synapses. These synapses are multidomain glycoproteins present throughout the body and CNS. Tripartite Synapses (TSPs) are responsible for eliciting the cycling of synaptic vesicles. When TSPs are taken out of an astrocyte-conditioned medium for retinal ganglion cell cultures, synaptogenic activity goes down. In neurons, α 2δ-1 subunit of VGCCs binds to astrocytes generated from TSPs. It activates neuronal activities that lead to the development of synapses.[58,59]

Astrocytes might increase synaptic activity, altering the strength of synapses and influencing learning and memory. N-methyl-D-aspartate (NMDA) receptors can be activated by astrocytes releasing D-serine, an NMDAR co-agonist, in response to Ca^{2+}.[60] Phagocytic activity results in synapse removal and allows precise neuronal connection. Astrocytes use several Epidermal Growth Factors (EGF)-like (MEGF-10) domains to promote synaptic phagocytosis. Astrocytes identify apoptotic cells by detecting "eat-me" (phosphatidylserine) signals in the outer leaflet of the target plasma membrane or by coating the target with an opsonin. The intracellular protein engulfment adaptor phosphotyrosine binding domain is involved in MEGF-10-mediated astrocytic phagocytosis. MEGF-10 leads to neuronal waste removal when astrocytes encapsulate the CNS synapses. Figure 3 represents the mechanism of formation and elimination of synapses by astrocytic signals.

Protein Aggregates Regulation Mediated by Astrocyte

The presence of β-Amyloid (Aβ) activates several signaling pathways in astrocytes. The asdvanced glycation end products receptors/NF-κB pathway that produces pro-inflammatory cytokines and chemokines is most important. IL-1, IL-6, TNFα, and inducible Nitric Oxide Synthase (iNOS) are examples of these cytokines.[61] Astrocytes can generate Aβ, which causes oxidative stress, Reactive Oxygen Production (ROS), and nitrogen species. In the degradation of Aβ plaques, reactive astrocytes play a dual role. Reactive astrocytes' phagocytic activity in the physiology of amyloid may help in the assessment of defective synapses or synaptic debris, repairing neuronal circuits, and lowering the influence of inflammation in impaired neurons. Amyloid Precursor Protein (APP)/Presenilin1 (PS1) plaques engulf the axonal connections in the hippocampus of mice and AD patients.[62] Extracellular monomeric and oligomeric Aβ endocytosis are carried out by astrocytes via actin polymerization.[63] Because of incomplete digestion, Transgenic (Tg)-ArcSwe mouse astrocytes, which have a lot of Aβ protofibrils, have a lot of toxic, partially shortened Aβ inside the cell and severe lysosomal dysfunction.[64]

Dysmetabolism and Dysfunction of Astrocytes in Neurodegeneration

Dysmetabolism of Astrocytes of Neurodegeneration

Astrocytes are a type of glial cell in the CNS that plays a critical role in supporting and maintaining the functions of neurons. Dysmetabolism refers to an abnormality in the metabolic processes of cells, which can have detrimental effects on their normal functions.[10] In the context of neurodegeneration, dysmetabolism of astrocytes has been implicated in the progression of various neurodegenerative disorders, including amyotrophic lateral sclerosis, Parkinson's disease, and AD.[65] Astrocytes are involved in numerous metabolic processes in the brain, including the

regulation of glucose metabolism, neurotransmitter uptake and recycling, antioxidant defense, and maintenance of the blood-brain barrier.[66] Dysfunction in these metabolic processes can disrupt normal brain function and contribute to the development and progression of neurodegenerative diseases.[67] In neurodegenerative disorders like AD, Parkinson's disease etc. dysmetabolism of astrocytes can manifest in several ways:

Impaired Glucose Metabolism

Astrocytes are responsible for taking up and metabolizing glucose in the brain through a process known as glycolysis.[68] In Alzheimer's disease, for example, there is evidence of reduced glucose metabolism in astrocytes, which may contribute to energy deficits in neurons and neuronal dysfunction.[69]

Mitochondrial Dysfunction

Astrocytes heavily rely on mitochondrial function to meet their energy demands. Impaired mitochondrial function in astrocytes can lead to reduced ATP production and energy deficits, which can impact their supportive functions and contribute to neurodegenerative processes.[70]

Impaired Glutamate and Neurotransmitter Handling

Astrocytes are involved in the uptake and recycling of neurotransmitters, including glutamate, which is a major excitatory neurotransmitter in the brain.[71] Dysfunctional astrocytes may exhibit impaired glutamate uptake and recycling, leading to increased extracellular glutamate levels and excitotoxicity, which can contribute to neuronal damage in neurodegenerative diseases.[72]

Oxidative Stress and Inflammation

Dysmetabolism in astrocytes can lead to increased production of ROS and oxidative stress. Elevated ROS levels can cause damage to cellular components and trigger inflammatory responses, leading to further disruption of astrocyte function and neurodegenerative processes.[73]

Dysfunction of Astrocytes in Neurodegeneration

The dysfunction of astrocytes has been found in several neurological disorders, including amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, and Huntington's disease.[74] There are several significant aspects that contribute to the dysfunction of astrocytes in neurodegenerative disorders.

Reactive Astrogliosis

Reactive astrogliosis refers to the response of astrocytes in the brain to pathogenic alterations, wherein these cells undergo a series of morphological and functional modifications.[75] Although the primary purpose of astrogliosis is to safeguard neurons and facilitate their repair, prolonged or excessive astrogliosis can potentially contribute to the process of neurodegeneration. Reactive astrocytes have the potential to display hypertrophy, modified gene expression, and atypical secretion of inflammatory chemicals.[76]

Impaired Glutamate Handling

Astrocytes play a crucial role in the regulation of glutamate levels inside synapses, facilitating the removal of excessive glutamate to maintain optimal neurotransmission and prevent excitotoxicity.[77] Astrocytes in neurodegenerative disorders may have compromised functionality in the uptake and clearance of glutamate, leading to elevated levels of extracellular glutamate. This elevation has the potential to adversely affect neuronal health.

Disrupted Calcium Homeostasis

Astrocytes are essential in the regulation of calcium homeostasis within the brain, ensuring its proper balance.[78] Astrocytes that are dysfunctional have the potential to display abnormal calcium signaling, resulting in disruptions in the regulation of intracellular calcium concentrations. The dysregulation of calcium in astrocytes has the potential to impact their supporting functions, interfere with neuronal communication, and play a role in the development of neurodegenerative conditions.[79]

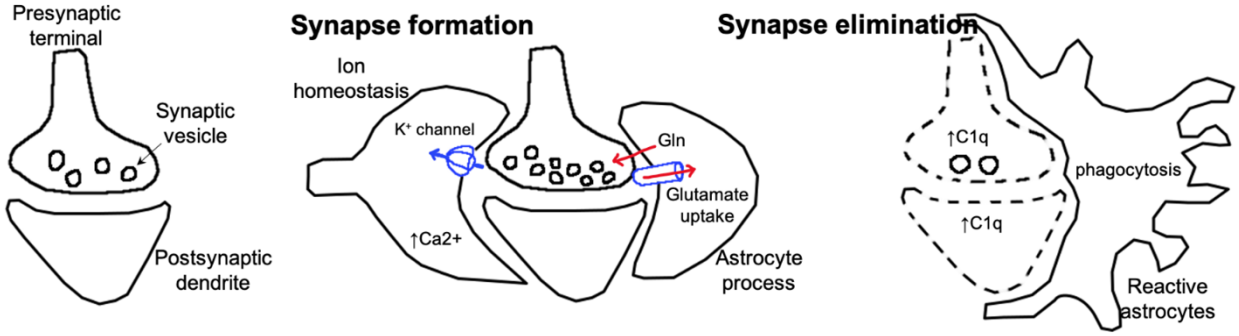

Figure 3: Astrocytic signals promote formation and elimination of synapse. Neurons forming less synaptic neurotransmitter vesicle without astrocytes. Astrocytes promotes maturation of pre and postsynaptic synapse elements. Upregulation of complement component C1q expression in neurons by reactive astrocytes, leads to elimination by astrocyte mediated phagocytosis. Re-drawn with permission from Kim *et al.*[10] Copyright© 2019, The Author(s) and MDPI.

Mitochondrial Dysfunction

Astrocytes exhibit elevated energy requirements, and any impairment in mitochondrial activity might detrimentally affect their metabolic capabilities. The presence of faulty mitochondria within astrocytes has the potential to result in a decrease in Adenosine Triphosphate (ATP) synthesis, an increase in oxidative stress, and a disruption of the antioxidant defense mechanisms. These factors collectively contribute to the malfunctioning of astrocytes and the subsequent development of neurodegenerative conditions.[80]

Altered Neurotrophic Support

Astrocytes provide neurotrophic support to neurons by secreting growth factors and promoting neuronal survival.[81] In neurodegenerative diseases, dysfunctional astrocytes may fail to provide adequate neurotrophic support, leading to neuronal vulnerability and degeneration.[82]

Inflammatory Responses

Astrocytes are involved in immune responses in the brain and can release pro-inflammatory cytokines and chemokines.[83] In neurodegenerative diseases, activated astrocytes may produce excessive inflammatory molecules, contributing to chronic neuroinflammation, which can exacerbate neuronal damage.[84]

Function of Astrocytes in Neurodegeneration

Neurodegenerative diseases show dysregulation of Ca^{2+} homeostasis due to excitotoxicity, disturbance of energy metabolism, oxidative stress, and altered Ca^{2+} regulating mechanisms in cells. Astrocytes are important in the development of the nervous system. Tenascin C and proteoglycans that are generated from astrocytes guide the development of axons. Astrocytes play an important role in synaptogenesis. Astrocytes play critical roles in the formation, maintenance, and destruction of synapses. Astrocytes are also important for neurotransmitter generation and control, the fabrication of antioxidants, the uptake of potassium, the metabolism of energy, and the coupling of nervous tissues. In both normal and pathological settings, astrocytes control neuronal activity by absorbing extracellular potassium and ensuring the maintenance of ion gradients, such as potassium, as a crucial mechanism for regulating cell volume. Astrocytes relate cerebral blood flow to neuronal energy requirements by releasing vasoactive chemicals like prostanoids. In response to neuronal activity, astrocytes provide essential metabolites like lactate to neurons. Astrocytes are necessary for neuronal survival. Astrocyte dysfunction can be a major cause of neurodegeneration. Hepatic encephalopathy, a neuropsychiatric condition resulting from liver disease, represents a potential scenario in which dysfunctional astrocytes may play a significant role in the development of neurological disorders. Astrocytic glutamine synthase plays a crucial role in the detoxification of elevated amounts of ammonia in the brain, which can arise as a result of acute or chronic liver disease.

Synaptic Function Control

By creating synaptically active molecules known as gliotransmitters, astrocytes play a direct role in synaptic transmission. Astrocytes release these chemicals in response to neuronal synaptic activity that stimulates astrocytes, resulting in Ca^{2+} waves and neuronal excitability. Astrocytes secrete gliotransmitters by lysosomal exocytosis. These lysosomes release ATP. This ATP blockage inhibits calcium propagation to adjacent astrocytes. The release of ATP by astrocytes regulates synaptic transmission and plasticity.

Control of Blood Flow

Astrocytes control the flow of blood reaching the nervous system. Changes in cerebral microcirculation affect neuronal activity.[85] In astrocytes, neuron signals create calcium waves, which release prostaglandins and nitric acid with dilation or constriction.[86,87]

CNS Energy and Metabolism

Astrocytes absorb glucose from the bloodstream and deliver it to neurons as an energy compound.5 Astrocytes are made of granules of glycogen in the CNS. These granules are present in ample amounts during the highest synaptic activity.[88] Glutamate modifies glycogen levels, and these glucose metabolites are transmitted to astrocytes by gap junctions.

Control of Circadian Rhythm

By communicating with neurons via adenosine, astrocytes contribute to sleep homeostasis and the sleep deficiency effect.[89-91]

Metabolism and Secretion of Lipids

The brain, as a vital organ of the body, has the highest amount of cholesterol. Changes in cholesterol metabolism lead to the development of neurological disorders like AD. Cholesterol levels are regulated in neurons and glial cells.[92,93] Instead of the blood, glial cells like astrocytes are responsible for producing lipids like cholesterol. In the CNS, LDL receptors are associated with signal transmission for lipoprotein ligand binding, which stimulates axonal growth and results in synaptogenesis.[94] Many essential functions due to astrocyte-produced lipids may affect CNS homeostasis.

Neuromodulation by Astrocytes

Astrocytes, a specific type of glial cell, play a crucial role in maintaining and regulating neuronal activity within the central nervous system. Neuromodulation refers to the manipulation or regulation of neuronal activity and neural networks using various techniques. While neurons have long been associated with neuromodulation, recent research suggests that astrocytes may play a significant role in this process.[95] The interaction between

astrocytes and neurons, referred to as "gliotransmission," has been widely acknowledged as a method via which astrocytes might affect synaptic transmission. During the process of gliotransmission, astrocytes are responsible for the release of a diverse range of signaling molecules, such as neurotransmitters and other substances. These released molecules have the potential to exert an influence on neighboring neurons.[96] This process may lead to alterations in the strength of synapses and overall activity within the network. Astrocyte has the capability to modulate brain function by regulating the levels of extracellular ions and neurotransmitters. These substances assist in maintaining optimal levels of ions such as potassium and neurotransmitters like glutamate, both of which are essential for proper brain function. Disruptions in these regulatory systems can have a profound influence on synaptic transmission and neuronal excitability. The ability of astrocytes to respond to alterations in neuronal activity through the release of several signaling molecules, including cytokines, growth factors, and chemokines, can also lead to neuromodulation. The potential influence of these substances on adjacent neurons and glial cells could potentially affect the overall functioning and adaptability of the entire network.10 Astrocytes have been increasingly recognized in recent research for their involvement in several neurological disorders, such as epilepsy, Alzheimer's disease, and depression. Dysfunctional interactions between astrocytes and neurons can give rise to the emergence and progression of these illnesses. The role of astrocytes in neuromodulation can be signified by:

Regulation of Synaptic Transmission

Astrocytes can actively regulate synaptic transmission by controlling the levels of neurotransmitters in the synaptic cleft.[97] They express neurotransmitter transporters, such as glutamate transporters, which remove excess neurotransmitters from the extracellular space, preventing their accumulation and maintaining optimal neurotransmitter levels. By regulating neurotransmitter availability, astrocytes can modulate synaptic strength and neuronal excitability.[98]

Release of Gliotransmitters

Astrocytes can release signaling molecules known as gliotransmitters in response to neuronal activity or specific stimuli. Gliotransmitters, including glutamate, ATP, D-serine, and various others, can act on neighboring neurons and modulate synaptic transmission. An instance of astrocytic glutamate release has the potential to stimulate presynaptic receptors, hence regulating the release of neurotransmitters. This process has a direct impact on synaptic plasticity and the overall activity of neuronal networks.[99]

Calcium Signalling

The phenomenon of calcium signaling in astrocytes is characterized by intricate dynamics, wherein alterations in the levels of calcium ions within the cell play a pivotal part in facilitating their neuromodulatory capabilities. The propagation of calcium signals in astrocytic networks and their subsequent impact on neighboring astrocytes and neurons can be attributed to neuronal activity or the release of neurotransmitters. The regulation of gliotransmitter release and modulation of synaptic activity can be achieved by calcium signaling in astrocytes.[100]

Metabolic Support

Astrocytes are crucial in facilitating metabolic support for neurons. Glucose is internalized and subsequently transformed into lactate, which can function as a viable energy source for neuronal cells. Astrocytes exert an indirect influence on neuronal activity and synaptic function by supplying neurons with metabolites that are rich in energy, so contributing to the process of neuromodulation.[101]

Regulation of Neurovascular Coupling

The regulation of neurovascular coupling involves the close association between astrocytes and blood vessels in the brain, as well as their active involvement in coordinating neuronal activity and local blood flow.[102] Astrocytes possess the capability to perceive alterations in neuronal activity and instigate signaling cascades, which subsequently result in the dilatation or constriction of blood vessels, thereby modulating the blood flow to accommodate the metabolic demands of active neurons.[103]

Reactive Astrogliosis-Neurotoxic and Neuroprotective Processes

The astrocytes' response to CNS injury is referred to as reactive astrogliosis. It is related to the alteration in astrocytes at functional, cellular, and molecular levels due to damage and CNS diseases.[104] Reactive gliosis includes everything from hypertrophy to proliferation and migration, which is a multi-staged response. Extracellular compounds released by reactive astrocytes include inflammatory modulators, chemokines, and cytokines, as well as different neurotrophic factors. Neuroprotective factors such as cytokines, transforming growth factor-β, and others are among these.[105,106]

The glial scar assists in the isolation of the injured area and prevents harm from spreading by limiting inflammatory cell infiltration. Although neurite growth can be inhibited by the chemicals produced by reactive scar-forming astrocytes.[107,108] Glial scar formation comprises tissue reorganization as well as long-term structural alterations that persist when the triggering stimulus is no longer present. Reactive astrocytes perform a variety of functions, including CNS cell protection by capturing potentially excitotoxic glutamate, glutathione release to combat oxidative stress, β-amyloid peptide degradation, and BBB repair.[109-111] These also limit inflammatory cells and the diffusion of infectious agents.[112-114]

Alzheimer's Disease

AD is a progressive brain disorder that gradually debilitates memory and thinking skills and eventually diminishes a person's ability to carry out routine tasks. Clinically, AD is defined as cognitive impairment in two or more domains, such as memory, language, arithmetic, orientation, and judgement. The impairment must be severe enough to cause social or occupational incapacity.

Astrocytes in Alzheimer's Disease

It is a leading cause of dementia.[115] Astrocytes are crucial in Aβ-peptide (amyloid-β) clearance, which prevents plaque formation. Higher Aβ concentrations lead to neurofibrillary tangle formation, which results in severe synaptic and neuronal loss.[116-118] On the other hand, peptides decrease the uptake of glutamate in astrocytes, which increases oxidative stress and activates the protein kinase cascade that mitogens activate. Pro-inflammatory cytokine levels are enhanced in the brain of AD patients by reactive astrocytes that respond to interleukin 6, interleukin 1β, and TNFα.[119,120]

During the progression of AD, astrocytes release feed-forward signals that stimulate other CNS cells to interact with neurons and microglia, contributing to the complex chain of events that ultimately results in neurodegeneration. Reactive astrocytes may play both protective and harmful roles in AD; atrophic astrocytes may lose their homeostatic capabilities. The role of astrocytes in β-amyloid breakdown and clearance influences AD progression (Figure 4).

Astrocytes are associated with the amyloid plaque in the cerebral cortex layer. Human amyloid may stimulate astrocytes, implying a link between the protein and astrocyte function modification. Neurodegeneration may lead to the accumulation of amyloid material derived from astrocytes. Due to the accumulation of these fragments, the astrocytes themselves may undergo cell death, which results in the formation of GFAP+ amyloid plaques. Astrocytes treated with Aβ improve the calcium-signaling waves in the middle of these cells. Calcium fluctuations occur in AD-expressing cells at lower levels of ATP and glutamate, which may not contribute to the death of neurons.

The involvement of genes conveyed by glial cells (such as oligodendrocytes, astrocytes, and/or microglia) is primarily responsible for AD.[17] Apolipoprotein E (APOE) is a critical genetic risk factor for late-onset AD. It causes β-amyloid deposition in the brain in healthy people.[122-125] Clusterin and Fermitin family member 2, two more genes linked to AD, are also primarily produced by astrocytes.[126-128] Reactive astrogliosis is commonly associated with AD. It can happen even before the formation of β-amyloid plaques, indicating the role of astrocytes in the etiology of AD. Morphological findings in the postmortem brains of AD patients revealed a strong relationship between β-amyloid and astrocyte deposition. When astrocytes are linked with senile plaques, they undergo morphological hypertrophy, as evidenced by thicker processes and enhanced production of GFAP (intermediate filament proteins), vimentin, nestin, and synemin.[129,130]

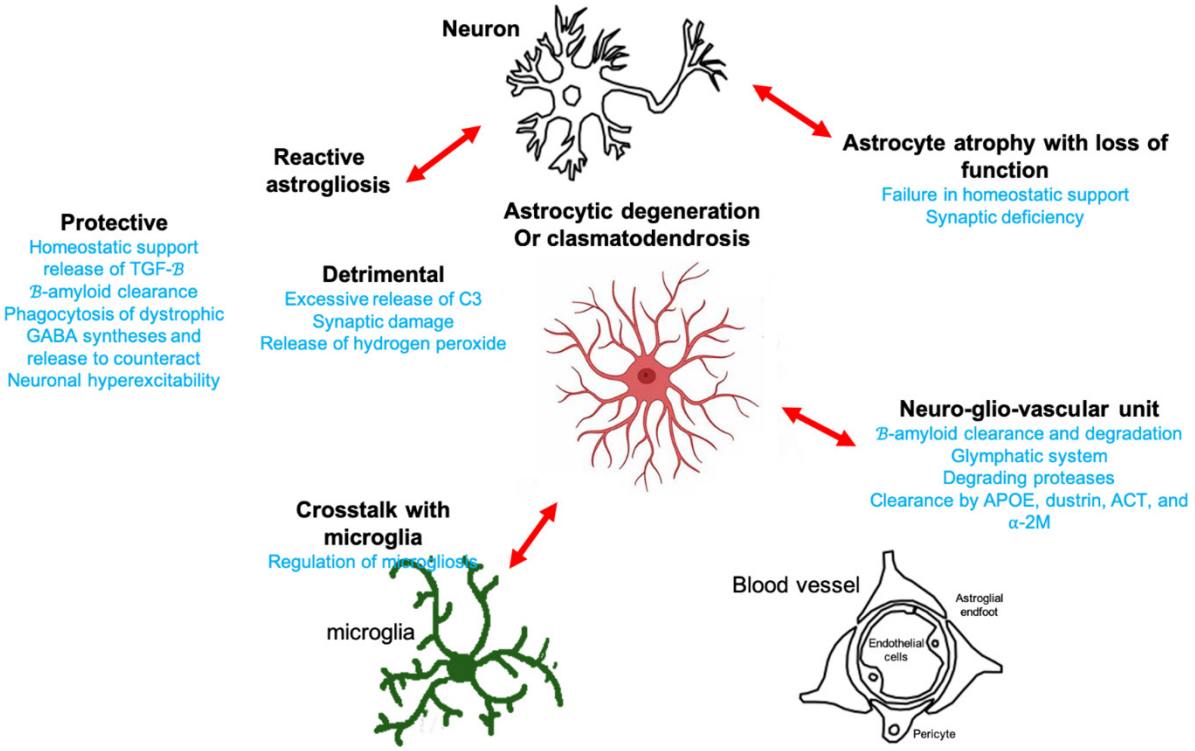

Figure 4: Representation of astrocyte's role in Alzheimer's disease. Image concept adopted from Preman *et al.*[121] Copyright© 2021, the author(s) and MDPI.

The brain of AD patients and AD mouse models have shown the presence of reactive astrocytes. Astrogliosis in AD, induced by pathological signals, could link damaged cells. Ca^{2+} release from the endoplasmic reticulum mediates β-amyloid-induced astrogliotic remodeling, which inhibits astrocytic reactivity. Astrocytes undergo modest isomorphic gliosis in AD with no overlapping of their domains. It demonstrates a defensive astrocytic response. In AD mice, inhibiting astrogliosis worsens pathophysiology and β-amyloid accumulation. In reactive astrocytes, calcium dynamics in the domain of plaques are abnormal. Hyperactivity of astrocyte Ca^{2+} may stimulate the release of harmful substances, change neuron-glia communication, and cause synaptic transmission impairment.[131-134] Postmortem brains of AD patients showed atrophic astrocytes in addition to significant astroglial reactivity. Precisely, severe disruption or complete disappearance of interlaminar astrocytes is the major characteristic of the human AD brain. Morphometric analysis of cells immunolabeled with antibodies against GFAP, S100, and GS showed that atrophic astrocytes are smaller and have thinner processes than GFAP, S100, and GS. In the presence of β-amyloid plaques in a mouse model, 3xTg-AD, atrophic astrocytes emerge in the Entorhinal Cortex (EC) after 1 month of life, and the atrophy lasts until 12 months of age.[135,136] Astroglial atrophy has been seen in mice with AD, such as PDAPP-J20 transgenic mice, 5xTG-AD mice, and Swiss 3 mice. When compared to normal cells, human astrocytes made from induced pluripotent stem cells (iPSC) in patients with familial and sporadic forms of AD show atrophic characteristics. Atrophy may result in the loss of astrocyte homeostatic functions, resulting in synaptic conditions, improved excitability, and/or degradation of the BBB. Neurodegenerative processes may harm astrocytes subsequent to clasmatodendrosis (described as distal fine process fragmentation and absence, as well as enlargement and vacuolation of the cell body).[137-140]

Astrocytes upregulate Amyloid Precursor Protein (APP) and beta-secretase 1 in a diseased brain. This could theoretically be involved in β-amyloid formation. However, there is no evidence that astrocytes are the primary generators of β-amyloid. Astrocytes play a major role in the clearance and elimination of β-amyloid by various mechanisms. Astrocytes take part in the glymaphatic system associated with the clearance of β-amyloid by expressing AQP4 water channels in their vascular end-feet. Astrocytes also produce β-amyloid degrading proteases, which disrupt peptides into minor pieces.[141-143]

Metalloendopeptidases like ECE1 and ECE2 (endothelin-converting enzymes 1 and 2), insulin-degrading enzyme, and neprilysin are expressed in astrocytes and cause the breakdown of monomeric β-amyloid species. Matrix metalloproteinases MMP-2 and MMP-9 break down both fibrillar and single-stranded β-amyloid in astrocytes. Extracellular proteins produced by astrocytes such as APOE, α1-antichymotrypsin, ApoJ/Clusterin, and α2-macroglobulin (α2-M) mediate clearance of β-amyloid. These proteins, singly or in combination with receptors (LRP1 and very low density lipoprotein receptor) stimulate the passage of β-amyloid across the BBB.[144,145]

APOE4-expressing astrocytes in mice and humans are less effective at clearing β-amyloid than APOE3 expressing astrocytes. APOE regulates the seeding and clearance of β-amyloid. APOE4 has a greater effect on seed development than APOE3. APOE influences plaque size and neuritic dystrophy. It does not influence the overall amyloid burden. APOE4 expression also causes pericyte degeneration, which facilitates BBB disintegration and APOE4 carrier damage.

Reactive astrocytes provide feedforward signals in AD by interacting with microglia and neurons, contributing to the neurodegenerative vicious cycle. In astrocytes, β-amyloid can trigger the NF-B pathway and produce C3 (a complement protein). β-amyloid phagocytosis modification occurs when C3 binds to microglial receptor C3aR. Neuronal receptor C3aR and C3 binding impair dendritic shape and network function, which contribute to the etiology of AD.[146] NF-κB and C3 cascades are stimulated in AD brains and AD mouse models. Microglia can activate astrocytes through the secretion of specific cytokines (IL-1α, TNFα, and C1q). Reactive astrocytes upregulate the expression of classic complement cascade genes, including C3, and lose their ability to support synapse growth and function, as well as phagocytoze synapses and myelin debris. C3-expressing astrocytes form about 60% of the astrocytes in the prefrontal cortex of Alzheimer's patients. These may play a role in neuronal degeneration.[147,148] In AD, reactive astrocytes play an important role in shifting the excitation-inhibition balance via the secretion of GABA. Astrocytes do not significantly contribute to GABA synthesis in a normal brain. GABA is synthesized by astrocytes in AD via the putrescine-MAO-B pathway.[121] Reactive astrocytes increase inhibition by secretion of GABA, which is probably a defensive response in contrast to neuronal hyperexcitability, which could result in AD progression universally. Increased MAO-B expression in astrocytes associated with AD leads to an increase in hydrogen peroxide generation, which can cause neuronal damage and death.[149,150]

AD progression also leads to deficiencies in metabolism and mitochondrial dysfunction. In AD brains, extensive transcriptomic and proteomic analyses have demonstrated a lack of mitochondrial bioenergetics. In the mouse brain, constant infusion of β-amyloid results in significant hydrogen peroxide enhancement, whereas β-amyloid contact with mouse astrocytes up-regulates superoxide dismutase and oxidative stress improvement.[151] It has been found that astrocytes in the AD mouse model produce an abnormally high amount of H_2O_2. β-amyloid causes mitochondrial depolarization, leading to the disruption of Ca^{2+} homeostasis. Astrocytic mitochondria are clustered around homeostatic transport sites. These provide

energy to Na^+/K^+ ATPase, which accumulates neurotransmitters, the most prominent of which is glutamate. A lowered ATP supply affects glutamate removal and results in excitotoxicity. Human astrocytes with the APOE4 genotype display reduced mitochondrial dynamics and function. Through transmitophagy, astrocytes support neuronal mitochondrial recycling when transfer between damaged neuronal mitochondria and astrocytes occurs and is degraded.[151-154] Furthermore, some evidence shows that the shuttling of astrocytic mitochondria into neurons aids neuronal bioenergetics, which precisely appears to enhance neuroprotection following stroke. Although neuronal-astrocytic transmitophagy provides neuroprotection in PD, it is unclear whether this process contributes to AD.

Astrocytes may contribute to the neuronal damage in human neurodegenerative disorders such as amyotrophic lateral sclerosis, PD, multiple sclerosis, and Huntington's disease. This indicates a direct role of these cells in neurodegeneration. Probably, astrocyte states and phenotypes vary between diseases and phases of the same disease. However, more investigations are needed to identify specific molecular pathways associated with precise phases of the disease.

Similarly, astrocytes can provide neuroprotection in various phases of AD. In response to β-amyloid, both astrogliosis and microgliosis enhance transforming growth factor β (TGF- β) secretion in glia, which in turn protects the β-amyloid toxicity of neurons and improves its clearance by microglia. β-amyloid plaques surrounding astrocytes in mice and AD patient brain show phagocytic activity by phagocytosing neuritic dystrophies. This suggests that astrocytes have a beneficial role in the aetiology of AD.[155]

AD is characterized by the accumulation of amyloid plaques outside cells and the formation of intraneuronal neurofibrillary tangles by modified tau. Mutations in PS1 and PS2 have been linked to the increased release of pathogenic amyloid from neurons. Tau is released by the neurons. Tau spreads when it is transferred from one set of neurons to another through synapses. The transcription of genes involved in the autophagic breakdown of tau is mediated by the transcription factor EB. Astrocytes, which express APP and beta-site APP-cleaving enzyme 1 (BACE1), can take up and remove Aβ produced by neurons, but they can also create Aβ. TNFα and Interferon gamma (IFN-γ)-induced increases in APP and BACE1 expression Red arrows showed an inhibitory effect.

Contribution of Astrocytes in Parkinson Disease

PD is described by dopaminergic neuron depletion in the substantia nigra and α-synuclein in a precise region of the brain stem, cortex, and spinal cord. It is a dopaminergic neurotransmission disruption in the basal ganglia. A reduction in dopaminergic neurons in the substantia nigra and cytoplasmic inclusions containing α-synuclein in residual dopaminergic neurons occur. Nonneuronal cells have neuropathological or neuroprotective activities in PD.[156] Aggregation development (responsible for cell-autonomous neuronal death) is influenced by the neuronal type and α-synuclein species. Astrocytes soak up axon terminals that deliver α-synuclein and allow intercellular transport to accumulate α-synuclein in astrocytes. This clearance mechanism is presented by α-synuclein localization in the astrocyte compartment. Inclusive uptake fails to degrade α-synuclein oligomers due to lysosome overload, causing deposit formation and mitochondrial damage.

In the early stages of sickness, astroglial acceptance and clearance of toxic α-synuclein molecules represent a neuroprotective mechanism. The data suggest that when aggregate formation keeps going on, the function of astrocytes is hurt by problems with endolysosomal degradation pathways and mitochondria. As a result, in PD or other synucleinopathies, a pathological buildup of α-synuclein in astrocytes causes injury to astrocytes by inducing loss of physiologic function and an increase in toxic activity.[157]

Unbalanced astrocyte-specific activity of progressive PD genes like DJ-1 and parkin is the contributory element to astrocyte dysfunction in PD. Interference in astrocyte-specific processes emphasizes many ways in which astrocytes can help to preserve brain conditions after damage. The protection of neurons from astrocytes against stress inducers is harmed when DJ-1 is down-regulated in an astrocyte-neuron co-culture system.[158] Antioxidants may not reverse the death of neurons. Drugs inhibiting mitochondrial complex I show neuroprotection. The release of glutathione or the upregulation of astrocytic heme oxygenase do not promote neuroprotection in this system. Thus, DJ-1's participation in astrocyte-mediated neuroprotection is restricted to the mitochondrial complex-I mediated mechanism and is unrelated to the oxidative stress response.

Parkin is a gene associated with PD. Perkin mutations are responsible for autosomal recessive Parkinsonism. Astrocytes and neurons have different levels of parkin. In stressed astrocytes, parkin is upregulated and redistributed, signifying that parkin might have a precise and astrocyte-specific role. Parkin mutations resulted in astrocyte impairment, followed by the death of neurons.[159,160] In PD, nitric oxide generation and glutathione depletion are similarly typical characteristics. Glutathione release is another way that astrocytes may protect neurons in a PD model. Glutathione formation increases when astrocytes are exposed to nitric oxide, and this high availability of glutathione by astrocytes could make neurons less sensitive to sensitive nitrogen strains. This pattern is followed in PD individuals with dopaminergic neurons in preserved areas holding glutathione-containing cells.

Astrocytes in Amyotrophic Lateral Syndrome

Amyotrophic Lateral Syndrome (ALS) is a progressive and serious disorder in which both upper and lower motor neurons of

the brain and spinal cord are dead, leading to muscle atrophy.[161] Multiple components of motor neuron cellular functioning are disrupted, and neuromuscular connections are destroyed. This has resulted in voluntary muscle paralysis. The fundamental pathogenic basis for ALS, as well as the precise insult that kills certain types of motor neurons, remain unknown. The astrocyte glutamate transporter EAAT2 is lost in both familial and sporadic ALS. Animal studies showed toxic effects such as loss of the EAAT2 transporter, which begins before the loss of motor neurons and is associated with reactive gliosis; transplanted ALS astrocytes generated reactive astrocytosis; the NMDA receptor coagonist d-serine has been hypothesized as a glia-derived enhancer of glutamate toxicity; and in ALS mice, the extent of d-serine and serine racemes, the enzyme generating d-serine, rises as the disease progresses, primarily in glia. Mitochondrial failure coupled with an increase in Reactive Oxygen Species (ROS) from ALS astrocytes is the hypothesized mechanism leading to neurotoxicity.[162–164]

IFN-α has been proposed to drive motor neuron-selective cell death through the activation of Lymphotoxin-Receptor (LT-R) by LIGHT as one of the multiple inflammatory mediators (prostaglandin D2, IFN-α, and TGF-α) implicated in astrocyte-neuron communication in ALS. IFN-α (treated human astrocytes are neurotoxic, most likely through a STAT3-dependent route.[165,166] In human tissues and transgenic ALS models, there is abundant evidence that astroglial abnormalities and functional dysfunction occur before clinical illness. These variations include reactive astrocytosis (G85R), glutamate passage loss, and GLT1 protein expression.

Multiple Sclerosis

Multiple sclerosis (MS) is a demyelinating inflammatory disease of the central nervous system in which glial cells play a crucial role. In multiple sclerosis plaques, astrocytes release IL-6 and lack-2 adrenergic receptors. It may act as an antigen-presenting cell, allow T cells to invade, and activate more easily. Repeatedly exposing astrocytes to inflammatory cytokines leads to uncontrolled inflammatory responses and elevated noradrenaline levels. This results in the formation of localized regions of myelin and axonal injury.

CONCLUSION

Astrocytes are required for the proper operation of the mammalian nervous system. The involvement of astrocytes in the pathophysiology of neurodegenerative diseases is most likely due to the loss of their normal homeostatic role and the onset of toxic functions in disease. In astrocytes, intracellular aggregates are observed in a variety of neurodegenerative disorders. The presence of these aggregates disrupts normal astrocytic functioning in a variety of ways, putting neuronal viability at risk. Astrocytes regulate K^+ buffering, glutamate clearance, brain antioxidant defense, intimate metabolic interactions with neurons, and neuronal excitability control. Astrocytes are involved in both exacerbation of damage and neuroprotective mechanisms in various clinical conditions, including AD, PD, ALS, and MS. Astrocytic dysfunction is linked to the cause of neurodegenerative diseases. Because of this, changing the activity of astrocytes could be an effective therapeutic approach to treat several chronic CNS problems.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

CNS: Central nervous system; **BBB:** Blood brain barrier; **GABA:** Gamma-Aminobutyric Acid; **Ach:** Acetylcholine; **ATP:** Adenosine triphosphate; **VGCC:** Voltage gated calcium channel; **TNFα:** Tumor necrosis factor alpha; **AQP4:** Aquaporin-4; **AD:** Alzheimer's disease; **PD:** Parkinson's disease; **TSPs:** Tripartite synapses; **NMDAR:** N-methyl-D-aspartate receptors; **ROS:** Reactive oxygen production; **RNS:** Reactive nitrogen species; **APP:** Amyloid precursor protein; **BACE1:** Beta-site **APP:** cleaving enzyme 1; **IFN:** interferon.

REFERENCES

1. Verkhratsky A, Nedergaard M. Astroglial cradle in the life of the synapse. Philos Trans R Soc Lond B Biol Sci. 2014; 369(1654): 20130595. doi: 10.1098/rstb.2013.0595, PMID 25225089.
2. Verkhratsky A, Nedergaard M. Physiology of astroglia. Physiol Rev. 2018; 98(1): 239-389. doi: 10.1152/physrev.00042.2016, PMID 29351512.
3. Giaume C, Koulakoff A, Roux L, Holcman D, Rouach N. Astroglial networks: a step further in neuroglial and gliovascular interactions. Nat Rev Neurosci. 2010; 11(2): 87-99. doi: 10.1038/nrn2757, PMID 20087359.
4. Houades V, Koulakoff A, Ezan P, Seif I, Giaume C. Gap junction-mediated astrocytic networks in the mouse barrel cortex. J Neurosci. 2008; 28(20): 5207-17. doi: 10.1523/JNEUROSCI.5100-07.2008, PMID 18480277.
5. Sofroniew MV, Vinters HV. Astrocytes: biology pathology. Adv Neuropathol. 2009; 110: 7-35. doi: 10.1007/s00401-009-0619-8.
6. Roux L, Benchenane K, Rothstein JD, Bonvento G, Giaume C. Plasticity of astroglial networks in olfactory glomeruli. Proc Natl Acad Sci U S A. 2011; 108(45): 18442-6. doi: 10.1073/pnas.1107386108, PMID 21997206.
7. Liddelow SA, Barres BA. Reactive astrocytes: production, function, and therapeutic potential. Immunity. 2017; 46(6): 957-67. doi: 10.1016/j.immuni.2017.06.006, PMID 28636962.
8. Emsley JG, Macklis JD. Astroglial heterogeneity closely reflects the neuronal-defined anatomy of the adult murine CNS. Neuron Glia Biol. 2006; 2(3): 175-86. doi: 10.1017/S1740925X06000202, PMID 17356684.
9. Oberheim NA, Takano T, Han X, He W, Lin JH, Wang F, *et al.* Uniquely hominid features of adult human astrocytes. J Neurosci. 2009; 29(10): 3276-87. doi: 10.1523/JNEUROSCI.4707-08.2009, PMID 19279265.
10. Kim Y, Park J, Choi YK. The role of astrocytes in the central nervous system focused on BK channel and heme oxygenase metabolites: a review. Antioxidants (Basel). 2019; 8(5): 121. doi: 10.3390/antiox8050121, PMID 31060341.
11. Kirischuk S, Parpura V, Verkhratsky A. Sodium dynamics: another key to astroglial excitability? Trends Neurosci. 2012; 35(8): 497-506. doi: 10.1016/j.tins.2012.04.003, PMID 22633141.
12. Rose CR, Verkhratsky A. Principles of sodium homeostasis and sodium signalling in astroglia. Glia. 2016; 64(10): 1611-27. doi: 10.1002/glia.22964, PMID 26919326.
13. Krnjević K, Schwartz S. Some properties of unresponsive cells in the cerebral cortex. Exp Brain Res. 1967; 3(4): 306-19. doi: 10.1007/BF00237557, PMID 6031163.

14. Bowman CL, Kimelberg HK. Excitatory amino acids directly depolarize rat brain astrocytes in primary culture. Nature. 1984; 311(5987): 656-9. doi: 10.1038/311656 a0, PMID 6148706.
15. Kettenmann H, Backus KH, Schachner M. Aspartate, glutamate and gamma-aminobutyric acid depolarize cultured astrocytes. Neurosci Lett. 1984; 52(1-2): 25-9. doi: 10.1016/0304-3940(84)90345-8, PMID 6152041.
16. Verkhratsky A, Orkand RK, Kettenmann H. Glial calcium: homeostasis and signaling function. Physiol Rev. 1998; 78(1): 99-141. doi: 10.1152/physrev.1998.78.1.99, PMID 9457170.
17. Verkhratsky A. Physiology of neuronal-glial networking. Neurochem Int. 2010; 57(4): 332-43. doi: 10.1016/j.neuint.2010.02.002, PMID 20144673.
18. Thomzig A, Wenzel M, Karschin C, Eaton MJ, Skatchkov SN, Karschin A, *et al.* Kir6.1 is the principal pore-forming subunit of astrocyte but not neuronal plasma membrane K-ATP channels. Mol Cell Neurosci. 2001; 18(6): 671-90. doi: 10.1006/mcne.2001.104 8, PMID 11749042.
19. Wu XF, Liu WT, Liu YP, Huang ZJ, Zhang YK, Song XJ. Reopening of ATP-sensitive potassium channels reduces neuropathic pain and regulates astroglial gap junctions in the rat spinal cord. Pain. 2011; 152(11): 2605-15. doi: 10.1016/j.pain.2011.08.003, PMID 21907492.
20. Rubini P, Pagel G, Mehri S, Marquardt P, Riedel T, Illes P. Functional P2X7 receptors at cultured hippocampal astrocytes but not neurons. Naunyn Schmiedebergs Arch Pharmacol. 2014; 387(10): 943-54. doi: 10.1007/s00210-014-1005-1, PMID 24961463.
21. de Rivero Vaccari JP, Dietrich WD, Keane RW. Activation and regulation of cellular inflammasomes: gaps in our knowledge for central nervous system injury. J Cereb Blood Flow Metab. 2014; 34(3): 369-75. doi: 10.1038/jcbfm.2013.227, PMID 24398940.
22. Sherwood CC, Stimpson CD, Raghanti MA, Wildman DE, Uddin M, Grossman LI, *et al.* Evolution of increased glia-neuron ratios in the human frontal cortex. Proc Natl Acad Sci U S A. 2006; 103(37): 13606-11. doi: 10.1073/pnas.0605843103, PMID 16938869.
23. Nedergaard M, Ransom B, Goldman SA. New roles for astrocytes: redefining the functional architecture of the brain. Trends Neurosci. 2003; 26(10): 523-30. doi: 10.10 16/j.tins.2003.08.008, PMID 14522144.
24. Carmignoto G, Pasti L, Pozzan T. T. On the role of voltage-dependent calcium channels in calcium signaling of astrocytes in situ. J Neurosci. 1998; 18(12): 4637-45. doi: 10.1523/JNEUROSCI.18-12-04637.1998, PMID 9614238.
25. Catterall WA, Perez-Reyes E, Snutch TP, Striessnig J, International Union of Pharmacology, XLVIII. International Union of Pharmacology. XLVIII. Nomenclature and structure-function relationships of voltage-gated calcium channels. Pharmacol Rev. 2005; 57(4): 411-25. doi: 10.1124/pr.57.4.5, PMID 16382099.
26. Cheli VT, Santiago González DA, Smith J, Spreuer V, Murphy GG, Paez PM. L-type voltage-operated calcium channels contribute to astrocyte activation *in vitro*. Glia. 2016; 64(8): 1396-415. doi: 10.1002/glia.23013, PMID 27247164.
27. Barres BA, Koroshetz WJ, Chun LLY, Corey DP. Ion channel expression by white matter glia: the type-1 astrocyte. Neuron. 1990; 5(4): 527-44. doi: 10.1016/0896-6273(90) 90091-S, PMID 1698397.
28. Puro DG, Hwang JJ, Kwon OJ, Chin H. Characterization of an L-type calcium channel expressed by human retinal Muller (glial) cells. Brain Res Mol Brain Res. 1996; 37(1-2): 41-8. doi: 10.1016/0169-328X(96)80478-5, PMID 8738134.
29. Choi YK, Kim JH, Lee DK, Lee KS, Won MH, Jeoung D, *et al.* Carbon monoxide potentiation of L-Type Ca2+ channel activity increases HIF-1alpha-independent VEGF expression via an AMPKalpha/SIRT1-mediated PGC-1alpha/ERRalpha axis. Antioxid Redox Signal. 2017; 27(1): 21-36. doi: 10.1089/ars.2016.6684, PMID 27554679.
30. Lee H, Choi YK. Regenerative effects of heme oxygenase metabolites on neuroinflammatory diseases. Int J Mol Sci. 2018; 20(1): 78. doi: 10.3390/ijms20010 078, PMID 30585210.
31. Alvarez S, Blanco A, Fresno M, Muñoz-Fernández MA. Nuclear factor-kappa B activation regulates cyclooxygenase-2 induction in human astrocytes in response to CXCL12: role in neuronal toxicity. J Neurochem. 2010; 113(3): 772-83. doi: 10.1111/j. 1471-4159.2010.06646.x, PMID 20180883.
32. Blanco A, Alvarez S, Fresno M, Muñoz-Fernández MÁ. Amyloid-beta induces cyclooxygenase-2 and PGE2 release in human astrocytes in NF-kappa B dependent manner. J Alzheimers Dis. 2010; 22(2): 493-505. doi: 10.3233/JAD-2010-100309, PMID 20847443.
33. Wang X, Lou N, Xu Q, Tian GF, Peng WG, Han X, *et al.* Astrocytic Ca2+ signaling evoked by sensory stimulation *in vivo*. Nat Neurosci. 2006; 9(6): 816-23. doi: 10.1038/nn170 3, PMID 16699507.
34. Brenner R, Jegla TJ, Wickenden A, Liu Y, Aldrich RW. Cloning and functional characterization of novel large conductance calcium-activated potassium channel beta subunits, hKCNMB3 and hKCNMB4. J Biol Chem. 2000; 275(9): 6453-61. doi: 10.1 074/jbc.275.9.6453, PMID 10692449.
35. Zhang FX, Gadotti VM, Souza IA, Chen L. Zamponi GW. BK potassium channels suppress Cavalih.gov/pubmed/10692449" \t "_blank" cium-activated potassium cha. Cell Rep. 2018; 22: 1956-64. doi: 10.1016/j.celrep.2018.01.073.
36. Girouard H, Bonev AD, Hannah RM, Meredith A, Aldrich RW, Nelson MT. Astrocytic endfoot Ca2+ and BK channels determine both arteriolar dilation and constriction. Proc Natl Acad Sci U S A. 2010; 107(8): 3811-6. doi: 10.1073/pnas.0914722107, PMID 20133576.
37. Filosa JA, Bonev AD, Straub SV, Meredith AL, Wilkerson MK, Aldrich RW, *et al.* Local potassium signaling couples neuronal activity to vasodilation in the brain. Nat Neurosci. 2006; 9(11): 1397-403. doi: 10.1038/nn1779, PMID 17013381.
38. Price DL, Ludwig JW, Mi H, Schwarz TL, Ellisman MH. Distribution of rSlo Ca2+-activated K+ channels in rat astrocyte perivascular endfeet. Brain Res. 2002; 956(2): 183-93. doi: 10.1016/S0006-8993(02)03266-3, PMID 12445685.
39. Chen D, Yu SP, Wei L. Ion channels in regulation of neuronal regenerative activities. Transl Stroke Res. 2014; 5(1): 156-62. doi: 10.1007/s12975-013-0320-z, PMID 24399572.
40. Wang S, Wang B, Shang D, Zhang K, Yan X, Zhang X. Ion channel dysfunction in astrocytes in neurodegenerative diseases. Front Physiol. 2022; 13: 814285. doi: 10.33 89/fphys.2022.814285, PMID 35222082.
41. Choudhury SP, Bano S, Sen S, Suchal K, Kumar S, Nikolajeff F, *et al.* Altered neural cell junctions and ion-channels leading to disrupted neuron communication in Parkinson's disease. npj Parkinsons Dis. 2022; 8(1): 66. doi: 10.1038/s41531-022-00324-9, PMID 35650269.
42. Hutchings CJ, Colussi P, Clark TG. Ion channels as therapeutic antibody targets. mAbs. 2019; 11(2): 265-96. doi: 10.1080/19420862.2018.1548232, PMID 30526315.
43. Abbott NJ, Rönnbäck L, Hansson E. Astrocyte-endothelial interactions at the blood-brain barrier. Nat Rev Neurosci. 2006; 7(1): 41-53. doi: 10.1038/nrn1824, PMID 16371949.
44. Eroglu C, Barres BA. Regulation of synaptic connectivity by glia. Nature. 2010; 468(7321): 223-31. doi: 10.1038/nature09612, PMID 21068831.
45. Hayakawa K, Esposito E, Wang X, Terasaki Y, Liu Y, Xing C, *et al.* Transfer of mitochondria from astrocytes to neurons after stroke. Nature. 2016; 535(7613): 551-5. doi: 10.1038 /nature18928, PMID 27466127.
46. Chung WS, Clarke LE, Wang GX, Stafford BK, Sher A, Chakraborty C, *et al.* Astrocytes mediate synapse elimination through MEGF10 and MERTK pathways. Nature. 2013; 504(7480): 394-400. doi: 10.1038/nature12776, PMID 24270812.
47. Tasdemir-Yilmaz OE, Freeman MR. Astrocytes engage unique molecular programs to engulf pruned neuronal debris from distinct subsets of neurons. Genes Dev. 2014; 28(1): 20-33. doi: 10.1101/gad.229518.113, PMID 24361692.
48. Müller CM, Best J. Ocular dominance plasticity in adult cat visual cortex after transplantation of cultured astrocytes. Nature. 1989; 342(6248): 427-30. doi: 10.1038 /342427a0, PMID 2586611.
49. Oberheim NA, Tian GF, Han X, Peng W, Takano T, Ransom B, *et al.* Loss of astrocytic domain organization in the epileptic brain. J Neurosci. 2008; 28(13): 3264-76. doi: 10 .1523/JNEUROSCI.4980-07.2008, PMID 18367594.
50. Heller JP, Rusakov DA. Morphological plasticity of astroglia: understanding synaptic microenvironment. Glia. 2015; 63(12): 2133-51. doi: 10.1002/glia.22821, PMID 25782611.
51. Anderson MA, Ao Y, Sofroniew MV. Heterogeneity of reactive astrocytes. Neurosci Lett. 2014; 565: 23-9. doi: 10.1016/j.neulet.2013.12.030, PMID 24361547.
52. Liu LR, Liu JC, Bao JS, Bai QQ, Wang GQ. Interaction of microglia and astrocytes in the neurovascular unit. Front Immunol. 2020; 11: 1024. doi: 10.3389/fimmu.2020.01024 , PMID 32733433.
53. Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, *et al.* Neurotoxic reactive astrocytes are induced by activated microglia. Nature. 2017; 541(7638): 481-7. doi: 10.1038/nature21029, PMID 28099414.
54. Takano T, Oberheim N, Cotrina ML, Nedergaard M. Astrocytes and ischemic injury. Stroke. 2009;40(S3):S8-S12. doi: 10.1161/STROKEAHA.108.533166, PMID 19064795.
55. Lo EH, Rosenberg GA. The neurovascular unit in health and disease: introduction. Stroke. 2009;40(S3):S2-3. doi: 10.1161/STROKEAHA.108.534404, PMID 19064779.
56. Choi YK, Maki T, Mandeville ET, Koh SH, Hayakawa K, Arai K, *et al.* Dual effects of carbon monoxide on pericytes and neurogenesis in traumatic brain injury. Nat Med. 2016; 22(11): 1335-41. doi: 10.1038/nm.4188, PMID 27668935.
57. Perea G, Navarrete M, Araque A. Tripartite synapses: astrocytes process and control synaptic information. Trends Neurosci. 2009; 32(8): 421-31. doi: 10.1016/j.tins.2009.0 5.001, PMID 19615761.
58. Christopherson KS, Ullian EM, Stokes CC, Mullowney CE, Hell JW, Agah A, *et al.* Thrombospondins are astrocyte-secreted proteins that promote CNS synaptogenesis. Cell. 2005; 120(3): 421-33. doi: 10.1016/j.cell.2004.12.020, PMID 15707899.
59. Eroglu C, Allen NJ, Susman MW, O'Rourke NA, Park CY, Özkan E, *et al.* Gabapentin receptor "https://www.ncbi.nlm.nih.gov/pubmed/15707899" \t "_blank" onic brain CNS synaptogenesis. Cell. 2009; 139(2): 380-92. doi: 10.1016/j.cell.2009.09.025, PMID 19818485.
60. Henneberger C, Papouin T, Oliet SH, Rusakov DA. Long-term potentiation depends on release of D-serine from astrocytes. Nature. 2010; 463(7278): 232-6. doi: 10.1038/ nature08673, PMID 20075918.
61. González-Reyes RE, Nava-Mesa MO, Vargas-Sánchez K, Ariza-Salamanca D, Mora-Muñoz L. Involvement of astrocytes in Alzheimer's disease from a neuroinflammatory and oxidative stress perspective. Front Mol Neurosci. 2017; 10: 427. doi: 10.3389/fnmol.2017.00427, PMID 29311817.
62. Jo S, Yarishkin O, Hwang YJ, Chun YE, Park M, Woo DH, *et al.* GABA from reactive astrocytes impairs memory in mouse models of Alzheimer's disease. Nat Med. 2014; 20(8): 886-96. doi: 10.1038/nm.3639, PMID 24973918.
63. Lee SJ, Seo BR, Koh JY. Metallothionein-3 modulates the amyloid beta endocytosis of astrocytes through its effects on actin polymerization. Mol Brain. 2015; 8(1): 84. doi: 10.1186/s13041-015-0173-3, PMID 26637294.
64. Kitazawa M, Cheng D, Tsukamoto MR, Koike MA, Wes PD, Vasilevko V, *et al.* Blocking IL-1 signaling rescues cognition, attenuates tau pathology, and restores neuronal

beta-catenin pathway function in an Alzheimer's disease model. J Immunol. 2011; 187(12): 6539-49. doi: 10.4049/jimmunol.1100620, PMID 22095718.

65. Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. Acta Neuropathol. 2010; 119(1): 7-35. doi: 10.1007/s00401-009-0619-8, PMID 20012068.
66. Kim T, Song B, Lee IS. Drosophila glia: models for human neurodevelopmental and neurodegenerative disorders. Int J Mol Sci. 2020; 21(14): 4859. doi: 10.3390/ijms21144859, PMID 32660023.
67. Oksanen M, Lehtonen S, Jaronen M, Goldsteins G, Hämäläinen RH, Koistinaho J. Astrocyte alterations in neurodegenerative pathologies and their modeling in human induced pluripotent stem cell platforms. Cell Mol Life Sci. 2019; 76(14): 2739-60. doi: 10.1007/s00018-019-03111-7, PMID 31016348.
68. Mulica P, Grünewald A, Pereira SL. Astrocyte-neuron metabolic crosstalk in neurodegeneration: A mitochondrial perspective. Front Endocrinol (Lausanne). 2021; 12: 668517. doi: 10.3389/fendo.2021.668517, PMID 34025580.
69. McCann MS, Maguire-Zeiss KA. Environmental toxicants in the brain: a review of astrocytic metabolic dysfunction. Environ Toxicol Pharmacol. 2021; 84(84): 103608. doi: 10.1016/j.etap.2021.103608, PMID 33556584.
70. Bantle CM, Hirst WD, Weihofen A, Shlevkov E. Mitochondrial dysfunction in astrocytes: A role in Parkinson's disease? Front Cell Dev Biol. 2020; 8: 608026. doi: 10.3389/fcell.2020.608026, PMID 33537300.
71. Gollihue JL, Norris CM. Astrocyte mitochondria: central players and potential therapeutic targets for neurodegenerative diseases and injury. Ageing Res Rev. 2020; 59: 101039. doi: 10.1016/j.arr.2020.101039, PMID 32105849.
72. Zhou Y, Danbolt NC. Glutamate as a neurotransmitter in the healthy brain. J Neural Transm (Vienna). 2014; 121(8): 799-817. doi: 10.1007/s00702-014-1180-8, PMID 24578174.
73. Satarker S, Bojja SL, Gurram PC, Mudgal J, Arora D, Nampoothiri M. Astrocytic glutamatergic transmission and its implications in neurodegenerative disorders. Cells. 2022;11(7):1139. doi: 10.3390/cells11071139, PMID 35406702.
74. Andersen JV, Markussen KH, Jakobsen E, Schousboe A, Waagepetersen HS, Rosenberg PA, *et al.* Glutamate metabolism and recycling at the excitatory synapse in health and neurodegeneration. Neuropharmacology. 2021; 196(196): 108719. doi: 10.1016/j.neuropharm.2021.108719, PMID 34273389.
75. Sofroniew MV. Astrogliosis. Cold Spring Harb Perspect Biol. 2014; 7(2):a020420. doi: 10.1101/cshperspect.a020420, PMID 25380660.
76. Verkhratsky A, Rodríguez JJ, Parpura V. Astroglia in neurological diseases. Future Neurol. 2013; 8(2): 149-58. doi: 10.2217/fnl.12.90, PMID 23658503.
77. Pekny M, Pekna M. Reactive gliosis in the pathogenesis of CNS diseases. Biochim Biophys Acta. 2016; 1862(3): 483-91. doi: 10.1016/j.bbadis.2015.11.014, PMID 26655603.
78. Li X, Li M, Tian L, Chen J, Liu R, Ning B. Reactive astrogliosis: implications in spinal cord injury progression and therapy. Oxid Med Cell Longev. 2020; 2020: 9494352. doi: 10.1155/2020/9494352, PMID 32884625.
79. Woo J, Cho H, Seol Y, Kim SH, Park C, Yousefian-Jazi A, *et al.* Power failure of mitochondria and oxidative stress in neurodegeneration and its computational models. Antioxidants (Basel). 2021; 10(2): 229. doi: 10.3390/antiox10020229, PMID 33546471.
80. Lampinen R, Belaya I, Saveleva L, Liddell JR, Rait D, Huuskonen MT, *et al.* Neuron-astrocyte transmitophagy is altered in Alzheimer's disease. Neurobiol Dis. 2022; 170: 105753. doi: 10.1016/j.nbd.2022.105753, PMID 35569719.
81. Shademan B, Avci CB, Karamad V, Soureh GJ, Olia JBH, Esmaily F, *et al.* The role of mitochondrial biogenesis in ischemic stroke. J Integr Neurosci. 2023; 22(4): 88. doi: 10.31083/j.jin2204088, PMID 37519159.
82. Tashiro R, Bautista-Garrido J, Ozaki D, Sun G, Obertas L, Mobley AS, *et al.* Transplantation of astrocytic mitochondria modulates neuronal antioxidant defense and neuroplasticity and promotes functional recovery after intracerebral hemorrhage. J Neurosci. 2022; 42(36): 7001-14. doi: 10.1523/JNEUROSCI.2222-21.2022, PMID 35970559.
83. Huang MLH, Chiang S, Kalinowski DS, Bae DH, Sahni S, Richardson DR. The role of the antioxidant response in mitochondrial dysfunction in degenerative diseases: cross-talk between antioxidant defense, autophagy, and apoptosis. Oxid Med Cell Longev. 2019; 2019: 6392763. doi: 10.1155/2019/6392763, PMID 31057691.
84. Rummel NG, Butterfield DA. Altered metabolism in Alzheimer disease brain: role of oxidative stress. Antioxid Redox Signal. 2022; 36(16-18): 1289-305. doi: 10.1089/ars.2021.0177, PMID 34416829.
85. Koehler RC, Gebremedhin D, Harder DR. Role of astrocytes in cerebrovascular regulation. J Appl Physiol (1985). 2006; 100(1): 307-17. doi: 10.1152/japplphysiol.00938.2005, PMID 16357084.
86. Gordon GRJ, Mulligan SJ, MacVicar BA. Astrocyte control of cerebrovasculature. Glia. 2007; 55(12): 1214-21. doi: 10.1002/glia.20543, PMID 17659528.
87. Metea MR, Newman EA. Glial cells dilate and constrict blood vessels:a mechanism of neurovascular coupling. J Neurosci. 2006; 26(11): 2862-70. doi: 10.1523/JNEUROSCI.4048-05.2006, PMID 16540563.
88. Phelps CH. Barbiturates induced glycogen accumulation in brain. An electron microscopic study. Brain Res. 1972; 39(1): 225-34. doi: 10.1016/0006-8993(72)90797-4.
89. Jackson FR. Glial cell modulation of circardian rhythms. Glia. 2011; 59(9): 1341-50. doi: 10.1002/glia.21097, PMID 21732426.
90. Lavialle M, Servière J. Circadian fluctuations in GFAP distribution in the Syrian hamster suprachiasmatic nucleus. NeuroReport. 1993; 4(11): 1243-6. doi: 10.1097/00001756-199309000-00008, PMID 8219021.
91. Halassa MM, Florian C, Fellin T, Munoz JR, Lee SY, Abel T, *et al.* Astrocytic modulation of sleep homeostasis and cognitive consequences of sleep loss. Neuron. 2009; 61(2): 213-9. doi: 10.1016/j.neuron.2008.11.024, PMID 19186164.
92. Karten B, Peake KB, Vance JE. Mechanisms and consequences of impaired lipid trafficking in Niemann-Pick type C1-deficient mammalian cells. Biochim Biophys Acta. 2009; 1791(7): 659-70. doi: 10.1016/j.bbalip.2009.01.025, PMID 19416638.
93. Wollmer MA. Cholesterol-related genes in Alzheimer's disease. Biochim Biophys Acta. 2010; 1801(8): 762-73. doi: 10.1016/j.bbalip.2010.05.009, PMID 20580938.
94. Hayashi H. Lipid metabolism and glial lipoproteins in the central nervous system. Biol Pharm Bull. 2011; 34(4): 453-61. doi: 10.1248/bpb.34.453, PMID 21467629.
95. Cunningham C, Dunne A, Lopez-Rodriguez AB. Astrocytes: heterogeneous and dynamic phenotypes in neurodegeneration and innate immunity. Neuroscientist. 2019; 25(5): 455-74. doi: 10.1177/1073858418809941, PMID 30451065.
96. Araque A, Navarrete M. Glial cells in neuronal network function. Philos Trans R Soc Lond B Biol Sci. 2010; 365(1551): 2375-81. doi: 10.1098/rstb.2009.0313, PMID 20603358.
97. Wahis J, Holt MG. Astrocytes, noradrenaline, αstrocytes, noradre and neuromodulation: evidence and unanswered questions. Front Cell Neurosci. 2021; 15: 645691. doi: 10.3389/fncel.2021.645691, PMID 33716677.
98. Auld DS, Robitaille R. Glial cells and neurotransmission: an inclusive view of synaptic function. Neuron. 2003; 40(2): 389-400. doi: 10.1016/s0896-6273(03)00607-x, PMID 14556716.
99. Fellin T. Communication between neurons and astrocytes: relevance to the modulation of synaptic and network activity. J Neurochem. 2009; 108(3): 533-44. doi: 10.1111/j.1471-4159.2008.05830.x, PMID 19187090.
100. Breitenseher MJ, Trattnig S, Gäbler C, Happel B, Bankier A, Kukla C, *et al.* [MRI in radiologically occult scaphoid fractures. Initial experiences with 1.0 Tesla (whole body-middle field equipment) versus 0.2 Tesla (dedicated low-field equipment)]. Radiologe. 1997; 37(10): 812-8. doi: 10.1007/s001170050287, PMID 9454275.
101. Williams NP, Kushwah N, Dhawan V, Zheng XS, Cui XT. Effects of central nervous system electrical stimulation on non-neuronal cells. Front Neurosci. 2022; 16: 967491. doi: 10.3389/fnins.2022.967491, PMID 36188481.
102. Slater C, Liu Y, Weiss E, Yu K, Wang Q. The neuromodulatory role of the noradrenergic and cholinergic systems and their interplay in cognitive functions: A focused review. Brain Sci. 2022; 12(7): 890. doi: 10.3390/brainsci12070890, PMID 35884697.
103. Nadim F, Bucher D. Neuromodulation of neurons and synapses. Curr Opin Neurobiol. 2014; 29: 48-56. doi: 10.1016/j.conb.2014.05.003, PMID 24907657.
104. Sofroniew MV. Molecular dissection of reactive astrogliosis and glial scar formation. Trends Neurosci. 2009; 32(12): 638-47. doi: 10.1016/j.tins.2009.08.002, PMID 19782411.
105. Silver J, Miller JH. Regeneration beyond the glial scar. Nat Rev Neurosci. 2004; 5(2): 146-56. doi: 10.1038/nrn1326, PMID 14735117.
106. Bush TG, Puvanachandra N, Horner CH, Polito A, Ostenfeld T, Svendsen CN, *et al.* Leukocyte infiltration, neuronal degeneration, and neurite outgrowth after ablation of scar-forming, reactive astrocytes in adult transgenic mice. Neuron. 1999; 23(2): 297-308. doi: 10.1016/S0896-6273(00)80781-3, PMID 10399936.
107. Faulkner JR, Herrmann JE, Woo MJ, Tansey KE, Doan NB, Sofroniew MV. Reactive astrocytes protect tissue and preserve function after spinal cord injury. J Neurosci. 2004; 24(9): 2143-55. doi: 10.1523/JNEUROSCI.3547-03.2004, PMID 14999065.
108. Voskuhl RR, Peterson RS, Song B, Ao Y, Morales LB, Tiwari-Woodruff S, *et al.* Reactive astrocytes form scar-like perivascular barriers to leukocytes during adaptive immune inflammation of the CNS. J Neurosci. 2009; 29(37): 11511-22. doi: 10.1523/JNEUROSCI.1514-09.2009, PMID 19759299.
109. Rothstein JD, Dykes-Hoberg M, Pardo CA, Bristol LA, Jin L, Kuncl RW, *et al.* Knockout of glutamate transporters reveals a major role for astroglial transport in excitotoxicity and clearance of glutamate. Neuron. 1996; 16(3): 675-86. doi: 10.1016/S0896-6273(00)80086-0, PMID 8785064.
110. Swanson RA, Ying W, Kauppinen TM. Astrocyte influences on ischemic neuronal death. Curr Mol Med. 2004; 4(2): 193-205. doi: 10.2174/1566524043479185, PMID 15032713.
111. Chen Y, Vartiainen NE, Ying W, Chan PH, Koistinaho J, Swanson RA. Astrocytes protect neurons from nitric oxide toxicity by a glutathione-dependent mechanism. J Neurochem. 2001; 77(6): 1601-10. doi: 10.1046/j.1471-4159.2001.00374.x, PMID 11413243.
112. Shih AY, Johnson DA, Wong G, Kraft AD, Jiang L, Erb H, *et al.* Coordinate regulation of glutathione biosynthesis and release by Nrf2-expressing glia potently protects neurons from oxidative stress. J Neurosci. 2003; 23(8): 3394-406. doi: 10.1523/JNEUROSCI.23-08-03394.2003, PMID 12716947.
113. Vargas MR, Johnson DA, Sirkis DW, Messing A, Johnson JA. Nrf2 activation in astrocytes protects against neurodegeneration in mouse models of familial amyotrophic lateral sclerosis. J Neurosci. 2008; 28(50): 13574-81. doi: 10.1523/JNEUROSCI.4099-08.2008, PMID 19074031.
114. Koistinaho M, Lin S, Wu XI, Esterman M, Koger D, Hanson J, *et al.* Apolipoprotein E promotes astrocyte colocalization and degradation of deposited amyloid-beta peptides. Nat Med. 2004; 10(7): 719-26. doi: 10.1038/nm1058, PMID 15195085.

115. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. Lancet. 2011; 377(9770): 1019-31. doi: 10.1016/S0140-6736(10)61349-9.
116. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002; 297(5580): 353-6. doi: 10.1126/science.1072994, PMID 12130773.
117. Selkoe DJ, American College of Physicians, American Physiological Society. Alzheimer disease: mechanistic understanding predicts novel therapies. Ann Intern Med. 2004; 140(8): 627-38. doi: 10.7326/0003-4819-140-8-200404200-00047, PMID 15096334.
118. Walsh DM, Selkoe DJ. Deciphering the molecular basis of memory failure in Alzheimer's disease. Neuron. 2004; 44(1): 181-93. doi: 10.1016/j.neuron.2004.09.010, PMID 15450169.
119. Pihlaja R, Koistinaho J, Kauppinen R, Sandholm J, Tanila H, Koistinaho M. Multiple cellular and molecular mechanisms are involved in human Au clearance by transplanted adult astrocytes. Glia. 2011; 59(11): 1643-57. doi: 10.1002/glia.21212, PMID 21826742.
120. Nagele RG, D'Andrea MR, Lee H, Venkataraman V, Wang HY. Astrocytes accumulate Astr and give rise to astrocytic amyloid plaques in Alzheimer disease brains. Brain Res. 2003; 971(2): 197-209. doi: 10.1016/S0006-8993(03)02361-8.
121. Preman P, Alfonso-Triguero M, Alberdi E, Verkhratsky A, Arranz AM. Astrocytes in Alzheimer's disease: pathological significance and molecular pathways. Cells. 2021; 10(3): 540. doi: 10.3390/cells10030540, PMID 33806259.
122. Arranz AM, De Strooper B. The role of astroglia in Alzheimer's disease: pathophysiology and clinical implications. Lancet Neurol. 2019; 18(4): 406-14. doi: 10.1016/S1474-4422(18)30490-3, PMID 30795987.
123. Yu JT, Tan L, Hardy J. Apolipoprotein E in Alzheimer's disease: an update. Annu Rev Neurosci. 2014; 37: 79-100. doi: 10.1146/annurev-neuro-071013-014300, PMID 24821312.
124. Holtzman DM, Bales KR, Tenkova T, Fagan AM, Parsadanian M, Sartorius LJ, *et al.* Apolipoprotein E isoform-dependent amyloid deposition and neuritic degeneration in a mouse model of Alzheimer's disease. Proc Natl Acad Sci U S A. 2000; 97(6): 2892-7. doi: 10.1073/pnas.050004797, PMID 10694577.
125. Verghese PB, Castellano JM, Garai K, Wang Y, Jiang H, Shah A, *et al.* ApoE influences amyloid-I (Ayl clearance despite minimal ApoE/Aa association in physiological conditions. Proc Natl Acad Sci U S A. 2013; 110(19): E1807-16. doi: 10.1073/pnas.1220484110, PMID 23620513.
126. Carter SF, Schöll M, Almkvist O, Wall A, Engler H, Langström B, *et al.* Evidence for astrocytosis in prodromal Alzheimer disease provided by 11C-deuterium-L-deprenyl: A multitracer PET paradigm combining 11C-Pittsburgh compound B and 18F-FDG. J Nucl Med. 2012; 53(1): 37-46. doi: 10.2967/jnumed.110.087031, PMID 22213821.
127. Rodriguez-Vieitez E, Saint-Aubert L, Carter SF, Almkvist O, Farid K, Schöll M *et al.* Diverging longitudinal changes in astrocytosis and amyloid PET in autosomal dominant Alzheimer's disease. Brain. 2016; 139(3): 922-36. doi: 10.1093/brain/awv404, PMID 26813969.
128. Schöll M, Carter SF, Westman E, Rodriguez-Vieitez E, Almkvist O, Thordardottir S, *et al.* Early astrocytosis in autosomal dominant Alzheimer's disease measured *in vivo* by multitracer positron emission tomography. Sci Rep. 2015; 5: 16404. doi: 10.1038/srep16404, PMID 26553227.
129. Serrano-Pozo A, Muzikansky A, Gómez-Isla T, Growdon JH, Betensky RA, Frosch MP, *et al.* Differential relationships of reactive astrocytes and microglia to fibrillar amyloid deposits in Alzheimer disease. J Neuropathol Exp Neurol. 2013; 72(6): 462-71. doi: 10.1097/NEN.0b013e3182933788, PMID 23656989.
130. Escartin C, Galea E, Lakatos A, O'Callaghan JP, Petzold GC, Serrano-Pozo A, *et al.* Reactive astrocyte nomenclature, definitions, and future directions. Nat Neurosci. 2021; 24(3): 312-25. doi: 10.1038/s41593-020-00783-4, PMID 33589835.
131. Kraft AW, Hu X, Yoon H, Yan P, Xiao Q, Wang Y, *et al.* Attenuating astrocyte activation accelerates plaque pathogenesis in APP/PS1 mice. FASEB J. 2013; 27(1): 187-98. doi: 10.1096/fj.12-208660, PMID 23038755.
132. Agulhon C, Sun MY, Murphy T, Myers T, Lauderdale K, Fiacco TA. Calcium Signaling and Gliotransmission in Normal vs. reactive Astrocytes. Front Pharmacol. 2012; 3: 139. doi: 10.3389/fphar.2012.00139, PMID 22811669.
133. Kuchibhotla KV, Lattarulo CR, Hyman BT, Bacskai BJ. Synchronous hyperactivity and intercellular calcium waves in astrocytes in Alzheimer mice. Science. 2009; 323(5918): 1211-5. doi: 10.1126/science.1169096, PMID 19251629.
134. Verkhratsky A, Rodríguez-Arellano JJ, Parpura V, Zorec R. Astroglial calcium signalling in Alzheimer's disease. Biochem Biophys Res Commun. 2017; 483(4): 1005-12. doi: 10.1016/j.bbrc.2016.08.088, PMID 27545605.
135. Yeh CY, Vadhwana B, Verkhratsky A, Rodríguez JJ. Early astrocytic atrophy in the entorhinal cortex of a triple transgenic animal model of Alzheimer's disease. ASN Neuro. 2011; 3(5): 271-9. doi: 10.1042/AN20110025, PMID 22103264.
136. Olabarria M, Noristani HN, Verkhratsky A, Rodríguez JJ. Age-dependent decrease in glutamine synthetase expression in the hippocampal astroglia of the triple transgenic Alzheimer's disease mouse model: mechanism for deficient glutamatergic transmission? Mol Neurodegener. 2011; 6: 55. doi: 10.1186/1750-1326-6-55, PMID 21801442.
137. Beauquis J, Vinuesa A, Pomilio C, Pavía P, Galván V, Saravia F. Neuronal and glial alterations, increased anxiety, and cognitive impairment before hippocampal amyloid deposition in PDAPP mice, model of Alzheimer's disease. Hippocampus. 2014; 24(3): 257-69. doi: 10.1002/hipo.22219, PMID 24132937.
138. Diniz LP, Tortelli V, Matias I, Morgado J, Bérgamo Araujo AP, Melo HM *et al.* Astrocyte transforming growth factor beta 1 protects synapses against As oligomers in Alzheimer's disease model. J Neurosci. 2017; 37(28): 6797-809. doi: 10.1523/JNEUROSCI.3351-16.2017, PMID 28607171.
139. Iram T, Trudler D, Kain D, Kanner S, Galron R, Vassar R, *et al.* Astrocytes from old Alzheimer's disease mice are impaired in As uptake and in neuroprotection. Neurobiol Dis. 2016; 96: 84-94. doi: 10.1016/j.nbd.2016.08.001, PMID 27544484.
140. Polis B, Srikanth KD, Elliott E, Gil-Henn H, Samson AO. L-norvaline reverses cognitive decline and synaptic loss in a murine model of Alzheimer's disease. Neurotherapeutics. 2018; 15(4): 1036-54. doi: 10.1007/s13311-018-0669-5, PMID 30288668.
141. Ries M, Sastre M. Mechanisms of Ae Clearance and degradation by glial cells. Front Aging Neurosci. 2016; 8: 160. doi: 10.3389/fnagi.2016.00160, PMID 27458370.
142. Lin YT, Seo J, Gao F, Feldman HM, Wen HL, Penney J, *et al.* APOE4 causes widespread molecular and cellular alterations associated with Alzheimer's disease phenotypes in human iPSC-derived brain cell types. Neuron. 2018;98(6):1141-54.e7. doi: 10.1016/j.neuron.2018.05.008.
143. Simonovitch S, Schmukler E, Bespalko A, Iram T, Frenkel D, Holtzman DM, *et al.* Impaired autophagy in APOE4 astrocytes. J Alzheimers Dis. 2016; 51(3): 915-27. doi: 10.3233/JAD-151101, PMID 26923027.
144. Huynh TV, Liao F, Francis CM, Robinson GO, Serrano JR, Jiang H, *et al.* Age-dependent effects of apoE reduction using antisense oligonucleotides in a model of βge-dependent. Neuron. 2017;96(5):1013-23.e4. doi: 10.1016/j.neuron.2017.11.014, PMID 29216448.
145. Liu CC, Zhao N, Fu Y, Wang N, Linares C, Tsai CW, *et al.* ApoE4 accelerates early seeding of amyloid pathology. Neuron. 2017;96(5):1024-32.e3. doi: 10.1016/j.neuron.2017.11.013, PMID 29216449.
146. Lian H, Zheng H. Signaling pathways regulating neuron-glia interaction and their implications in Alzheimer's disease. J Neurochem. 2016;136(3):475-91. doi: 10.1111/jnc.13424, PMID 26546579.
147. Lian H, Yang L, Cole A, Sun L, Chiang AC, Fowler SW, *et al.* NF-kB-activated astroglial release of complement c3 compromises neuronal morphology and function associated with Alzheimer's disease. Neuron. 2015;85(1):101-15. doi: 10.1016/j.neuron.2014.11.018, PMID 25533482.
148. Fatoba O, Itokazu T, Yamashita T. Complement cascade functions during brain development and neurodegeneration. FEBS Journal. 2022; 289(8): 2085-109. doi: 10.1111/febs.15772, PMID 33599083.
149. Garaschuk O, Verkhratsky A. GABAergic astrocytes in Alzheimer's disease. Aging. 2019; 11(6): 1602-4. doi: 10.18632/aging.101870, PMID 30877782.
150. Chun H, Im H, Kang YJ, Kim Y, Shin JH, Won W, *et al.* Severe reactive astrocytes precipitate pathological hallmarks of Alzheimer's disease via H_2O_2- production. Nat Neurosci. 2020; 23(12): 1555-66. doi: 10.1038/s41593-020-00735-y, PMID 33199896.
151. Sarkar P, Zaja I, Bienengraeber M, Rarick KR, Terashvili M, Canfield S, *et al.* Epoxyeicosatrienoic acids pretreatment improves amyloid beta-induced mitochondrial dysfunction in cultured rat hippocampal astrocytes. Am J Physiol Heart Circ Physiol. 2014; 306(4):H475-84. doi: 10.1152/ajpheart.00001.2013, PMID 24285116.
152. Kaminsky YG, Kosenko EA. Effects of amyloid-beta peptides on hydrogen peroxide-metabolizing enzymes in rat brain *in vivo*. Free Radic Res. 2008; 42(6): 564-73. doi: 10.1080/10715760802159057, PMID 18569014.
153. Abramov AY, Canevari L, Duchen MR. β RhenriNK "https://www.ncbi.nlm.nih.gov/pubmed/18569014" \t "_blank" itochondrial dysfunction in cultured rat hippocampal astrocyNADPH oxidase. J Neurosci. 2004; 24(2): 565-75. doi: 10.1523/JNEUROSCI.4042-03.2004, PMID 14724257.
154. Genda EN, Jackson JG, Sheldon AL, Locke SF, Greco TM, O'Donnell JC, *et al.* Co-compartmentalization of the astroglial glutamate transporter, GLT-1, with glycolytic enzymes and mitochondria. J Neurosci. 2011; 31(50): 18275-88. doi: 10.1523/JNEUROSCI.3305-11.2011, PMID 22171032.
155. Gomez-Arboledas A, Davila JC, Sanchez-Mejias E, Navarro V, Nuñez-Diaz C, Sanchez-Varo R, *et al.* Phagocytic clearance of presynaptic dystrophies by reactive astrocytes in Alzheimer's disease. Glia. 2018; 66(3): 637-53. doi: 10.1002/glia.23270, PMID 29178139.
156. Lücking CB, Brice A. Alpha-synuclein in Parkinson's disease. Cell Mol Life Sci. 2000; 57(13-14): 1894-908. doi: 10.1007/PL00000671, PMID 11215516.
157. Filippini A, Gennarelli M, Russo I. Alpha-synuclein and glia in Parkinson's disease: A beneficial or a detrimental duet for the endo-lysosomal system? Cell Mol Neurobiol. 2019; 39(2): 161-8. doi: 10.1007/s10571-019-00649-9, PMID 30637614.
158. Bonifati V, Rizzu P, Van Baren MJ, Schaap O, Breedveld GJ, Krieger E, *et al.* Mutations in the DJ-1 gene associated with autosomal recessive early-onset Parkinsonism. Science. 2003; 299(5604): 256-9. doi: 10.1126/science.1077209, PMID 12446870.
159. Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, *et al.* Mutations in the parkin gene cause autosomal recessive juvenile Parkinsonism. Nature. 1998; 392(6676): 605-8. doi: 10.1038/33416, PMID 9560156.
160. Imai Y, Soda M, Takahashi R. Parkin suppresses unfolded protein stress-induced cell death through its E3 ubiquitin-protein ligase activity. J Biol Chem. 2000; 275(46): 35661-4. doi: 10.1074/jbc.C000447200, PMID 10973942.

161. Kiernan MC, Vucic S, Cheah BC, Turner MR, Eisen A, Hardiman O, *et al.* Amyotrophic lateral sclerosis. Lancet. 2011; 377(9769): 942-55. doi: 10.1016/S0140-6736(10)61156-7.

162. Rothstein JD, Martin LJ, Kuncl RW. Decreased glutamate transport by the brain and spinal cord in amyotrophic lateral sclerosis. N Engl J Med. 1992; 326(22): 1464-8. doi: 10.1056/NEJM199205283262204, PMID 1349424.

163. Papadeas ST, Kraig SE, O'Banion C, Lepore AC, Maragakis NJ. Astrocytes carrying the superoxide dismutase 1 (SOD1G93A) mutation induce wild-type motor neuron degeneration *in vivo*. Proc Natl Acad Sci U S A. 2011; 108(43): 17803-8. doi: 10.1073/pnas.1103141108, PMID 21969586.

164. Sasabe J, Chiba T, Yamada M, Okamoto K, Nishimoto I, Matsuoka M, *et al.* D-serine is a key determinant of glutamate toxicity in amyotrophic lateral sclerosis. EMBO J. 2007; 26(18): 4149-59. doi: 10.1038/sj.emboj.7601840, PMID 17762863.

165. Di Giorgio FP, Boulting GL, Bobrowicz S, Eggan KC. Human embryonic stem cell-derived motor neurons are sensitive to the toxic effect of glial cells carrying an ALS causing mutation. Cell Stem Cell. 2008; 3(6): 637-48. doi: 10.1016/j.stem.2008.09.017, PMID 19041780.

166. Phatnani HP, Guarnieri P, Friedman BA, Carrasco MA, Muratet M, O'Keeffe S, *et al.* Intricate interplay between astrocytes and motor neurons in ALS. Proc Natl Acad Sci U S A. 2013; 110(8): E756-65. doi: 10.1073/pnas.1222361110, PMID 23388633.

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