v. 5, n. 29, 2025

International Journal of Health Science

Acceptance date: 10/09/2025

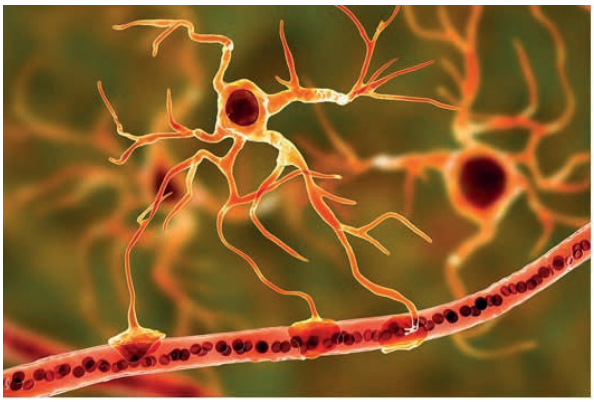
ASTROCYTES: FROM PROTAGONISM TO DEFICITS

Fabiano de Abreu Agrela Rodrigues
Post-PhD in Neuroscience, specializing in Genomics
Heráclito Research and Analysis Center (CPAH), Department of Neuroscience and Genomics, Brazil & Portugal
https://orcid.org/0000-0002-5487-5852

Abstract: This article uses a literature review methodology to gather, analyze, and synthesize the latest information on the various functions performed by glial cells, focusing on astrocytes as essential for the proper functioning of the neural system. It was found that astrocytes have the functions of isolating, sustaining, and nourishing neurons; they are an integral and essential part of the passive homeostatic control of synaptic conditions and function; they are important multifunctional regulators of neurometabolic coupling; they control blood flow in the central nervous system through the release and production of vasoactive molecules; and are also primary mediators at the site of blood flow in relation to various neuronal activities of the central nervous system. They perform detoxification and phagocytosis, have immune functions, and play an essential role in the formation and maintenance of the blood-brain barrier (BBB) and, consequently, in the necessary modulations in immuno-inflammatory responses. Recent findings indicate that astrocyte deficiency and malfunction are directly related to Alzheimer's disease and some forms of epilepsy, and are also correlated with memory and learning problems.
Keywords: astrocytes, central nervous system, glial cells, brain.

INTRODUCTION

This article aims to conduct a literature review of the main scientific documents that comprise the most current studies on glial cells, more specifically astrocytes. Thus, the objective is to gather the main information related to astrocytes in order to bring together scientific knowledge and publications for better evaluation by future researchers. In this way, we intend to report on studies and evaluations of astrocytes and their possible activities and functions, summarizing the latest scientific findings to assist future research in the field.



Astrocytes - Credit: Dr_Microbe / iStock

In addition, the main diseases directly related to astrocytes and their activities, their various fundamental purposes in the Central Nervous System (CNS), and the consequences of their dysregulation will be addressed. To this end, we present a study conducted on rats in culture at different stages of development, the first group consisting of adults (between 90 days of age) and another group consisting of aged rats (around 180 days of age). Among the main diseases related to astrocyte deficits and malfunction are Alzheimer's disease and some types of epileptic seizures.

2. DEVELOPMENT

The original descriptions of the cellular basis of the nervous system pointed to neurons as cells that form the main elements involved in information transfer processes in the brain. This understanding has probably prevailed over the last few decades because neurons extend to various sensory and muscular organs and even glands. Furthermore, in accordance with what was considered until then, electricity was recognized by the scientific community as a key element in the functioning of the nervous system and, therefore, neurons, being electrically excitable cells, would also be primarily responsible for the passage of information. This thinking sustained ideas that dominated the field until recently, when new discoveries brought interesting data for a new understanding. As discussed by Goergen and Cruz (2012):

> Glial cells, among which astrocytes are the most abundant, have historically been understood as cells that serve to isolate, sustain, and nourish neurons, but their functions are becoming increasingly clear, although there are still paradigms to be broken regarding their functions (GEORGEN and CRUZ, 2012, p. 1).

In other words, the function of glial cells, particularly astrocytes, has been examined as merely structural, since, according to Araque and Navarrete (2010), they probably do not have long connection processes between the sensory organs and effectors, as described above.

Until then, it was believed that astrocytes were merely passive cells responsible for providing "trophic, structural, and metabolic support to neurons, without actively participating in information processing by the nervous system (Zonta et al., 2003; Metea & Newman, 2006b; Gordon et al., 2007b).

In the early stages of research on the brain and the cells that make up the central nervous system, astrocytes were understood as mere auxiliaries to neuronal cells, serving only as a kind of coating for neurons (Kettenmann & Verkhratsky 2008).

Despite this initial impression, which was held for decades by the scientific community, advances in studies and instruments have shown that astrocytes are highly versatile cells that perform a variety of complex activities essential to the proper functioning of the central nervous system (Nedergaard et al. 2003; Maragakis & Rothstein 2006; Wang & Bordey 2008).

Thus, the latest evidence provided by Araque and Navarrete (2010) has shed new light on the conceptual situation of astrocytes as performing a passive role, merely providing adequate conditions for neural functioning.

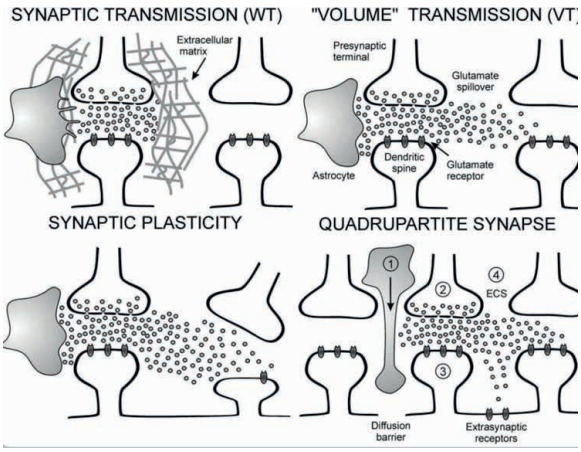
The neglect of astrocytes as fundamental to neural functioning was mainly due to the lack of electrical excitation of these cells, placing them in a peripheral position in terms of neuronal activity. However, research conducted by Perea and Araque (2005), Cornell-Bell et al. (1990), and Charles et al. (1991) using Ca2+-sensitive fluorescent dyes, it was possible to monitor cell ions at the intracellular level and demonstrate that astrocytes exhibit sensitivity based on Ca2+ variations in the cytosol, rather than electrical changes. Thus, with the advancement of studies, it was possible to verify that they play an active role as brain information processors (Araque and Navarrete, 2010).

In this way, recent studies have been able to establish the signaling of the bidirectional existence of neurons and astrocytes pointed out by cellular excitability based on calcium demonstrated by astrocytes, triggering neuronal and synaptic activity. All this is due to the activation of neurotransmitter receptors manifested by astrocytes (Perea and Araque, 2005).

Glutamate, ATP, and serine, responsible for regulating neuronal excitability and synaptic transmission, known as gliotransmitters, are activated by increased calcium in astrocytes, which stimulates their release. Such scientific advances have made it possible to work with a new synaptic physiological concept, forming what is known today as the tripartite synapse, conceptualized from the exchange of information between neuronal synaptic elements and astrocytes (Haydon, 2001; Volterra & Bezzi, 2002; Perea et al., 2009).

On this subject, Goergen and Cruz (2012) reveal that:

> The process of synapse formation and maturation, known as neuronal plasticity, is an old concept, and according to it, interneuronal synapses are continuously built and strengthened as part of human development, changing with each new stimulus. It was always thought that this phenomenon was purely neuronal, but it has been found that astrocytes are also involved. (GEORGEN and CRUZ, 2012)



Consequently, astrocytes have come to be recognized as an integral and essential part of synaptic exchanges, not only responsible for passive homeostatic control of conditions but also active in synaptic function (Araque et al., 1999; Perea et al., 2009).

According to Bellaver (2015), astrocytes "are multifunctional regulators of neurometabolic coupling" (Bellaver, 2015, p. 9). Stobart and Anderson (2013) reinforce that they are in a strategic position in brain processes in which they maintain contact with both blood vessels and neurons themselves, being able to capture energy substrates from the blood and direct them to neurons, providing sufficient energy for the full functioning of neural activities.

In this sense, Gordon et al (2007) demonstrate that astrocytes in this position, which are in constant contact and have multiple bidirectional interactions with blood vessels, are also capable of controlling blood flow in the central nervous system through the release and production of vasoactive molecules.

Subsequently, important studies have found that these cells are primary mediators at the site of blood flow in relation to various neuronal and y activities of the central nervous system (Koehler et al., 2009). The reflections of Goergen and Cruz (2012) summarize that:

> The blood-brain barrier, in whose functioning astrocytes act physically and metabolically, is a membrane-like structure that acts primarily to protect the central nervous system from harmful agents present in the blood, while allowing the normal functioning of the brain, which includes the need for exchanges with the circulatory system.

Bignami (1991) indicates that the main functions performed by astrocytes can be understood on two fronts, the first being to support the brain's neurons, both nutritionally and structurally, and the second being to participate functionally in the composition of the blood-brain barrier. Montgomery (1994) points out in his propositions that astrocytes participate in other functions besides those described above, namely detoxification, phagocytosis, and immune functions.

According to Goergen and Cruz (2012), astrocytes can be classified into two groups: protoplasmic or fibrous. The authors point out that "protoplasmic astrocytes are found in the gray matter and have processes that involve synapses and blood vessels" (Goergen and Cruz, 2012). They also indicate that fibrous astrocytes "are present in the white matter and come into contact with Ranvier's nodes and blood vessels." The authors then point out that "the concentration of various ions and neurotransmitters in the synaptic clefts is balanced by astrocytes, which are also capable of releasing their own substances, gliotransmitters" (Goergen and Cruz, 2012).

Thus, it is understood that astrocytes are responsible for regulating the formation of synapses, also acting to modulate their activities. According to Ota et al. (2013), there is a high probability that these cells are fundamental in the exercise of memory and also in the learning process. These processes are mainly located in the hippocampus area of the brain.

Furthermore, the probable functions identified for astrocytes are diverse, as demonstrated by Zhang and Pardridge (2001) and Ca-

bezas et al. (2014) in their studies. The results of the research allow us to conjecture about the participation of astrocytes with essential performance in the formation and maintenance of the blood-brain barrier (BBB) and, consequently, the necessary modulations in immuno-inflammatory responses. The movement of electrolytes, xenobiotics, and also the passage of immune system cells between the parenchymal and systemic circulation of the central nervous system maintain adequate variables in the brain environment for neural functions.

Bellaver et al (2014), considering the hippocampus as a relevant area for research into the pathophysiological processes of aging and the fundamental role of astrocytes involved in this sense, performed a routine protocol on primary cultures of hippocampal astrocytes in adult and aged rats. The former were all in the 90-day range, the latter in the 180-day range.

This made it possible to analyze in their study what happens to glial cells during aging. The author reveals that, in addition, "age-dependent changes in astrocytic functionality were observed through the evaluation of redox homeostasis, inflammatory response, and signaling pathways" (Bellaver et al., 2014, p. 75).

The author indicates that no significant behavioral changes were detected between adult and aged cultures, but changes were detected in the cellular, molecular, and neurochemical indices evaluated, revealing important data for understanding astrocytes in brain function (Bellaver et al., 2014).

Fabricius et al. (2013) and Rodrigues-Arellano et al. (2015) revealed in their studies that the number of astrocytes does not decrease with age, but there is still no consensus in the scientific community on the pattern of expression in cultured astrocytes.

Despite this, Sampedro-Piquero et al. (2014) demonstrated a significant increase, as a function of age, in reflections of adaptive astroglial plasticity, which, according to the author, would refer to cognitive changes that would coincide with astroglial transformations.

On the other hand, Rodriguez et al. (2014) demonstrated that astroglial degeneration and atrophy can be an important feature with pathological relevance. The author points out that "since atrophic astrocytes reduce support for neural networks, this effect is detected in the early stages of several neurodegenerative diseases" (Rodriguez et al. 2014).

In light of these studies, Menet et al. (2001) confirm that:

> The exact physiological role of GFAP and vimentin in astrocytes is not yet fully understood, but it is known that these proteins appear to be involved in maintaining the shape, mechanical stability, cytoarchitecture, and synaptic functions of the CNS, processes that are strongly affected by age (MENET et al., 2001, p. 84).

The importance of astrocytes in brain development is noteworthy, since when immature they are expressed by vimentin, which is gradually replaced by the GFAP (glial fibrillary acidic protein) gene as astrocytes mature (Bramanti et al, 2010). It should be noted that GFAP has been widely recognized by the scientific community as a true differential marker of astrocytes, being composed of the main protein that integrates the intermediate filaments between mature astrocytes (Bramanti et al., 2010).

According to the aforementioned experiment, it was possible to verify that among the primary cultures of astrocytes in the hippocampus area of the brains of adult and aged rats, as described, there was a lower expression of GFAP when associated with astrocytes presented by neonatal cultures. Therefore, it appears that GFAP is expressed progressively according to brain development. Based on the research, it was possible to report a significant

International Journal of Health Science ISSN 2764-0159 DOI https://doi.org/10.22533/at.ed.1595292515089

decrease in vimentin protein. In agreement with the above, the results demonstrate co--expression of GFAP and vimentin in hippocampal astrocyte cultures, thus suggesting the suitability of the culture model presented for aging studies (Menet et al. 2001; Pertusa et al. 2007; Souza et al. 2013).

Despite advances, Bellaver et al. indicate that the physiological functions performed by GFAP and vimentin in astrocytes are not yet widely understood. However, it is still possible to state that these proteins appear to be involved in the shape, mechanical stability, cytoarchitecture, and synaptic functions of the central nervous system. As Menet et al. (2001) indicate, all the functions described above are closely related to the age of the cultures studied.

Consequently, Danbolt (2001) and Banerjee et al. (2008) agree in their investigations of glutamatergic metabolism and the expression of other astrocytic markers important in cerebral plastic processes, and therefore in the process of development and aging ( ).

Furthermore, Segovia et al. (2001) and Izquierdo et al (2006) go further and conclude that these markers also influence learning and memory processes, since they are related to brain plasticity. It is evident that when hyperstimulation of the glutamatergic system occurs as a result of high levels of glutamate present in synaptic clefts, there is significant damage to the brain.

Several studies, such as those by Gardoni and Luca (2006), Eulenburg and Gomenza (2010), and Pivovarova and Andrews (2010) increasingly point out that the situation described above, known as glutamatergic excitotoxicity, is directly implicated in the presence of pathologies such as Parkinson's, Alzheimer's, multiple sclerosis, and some types of epilepsy.

According to Squire et al. (1990), in accordance with animal experiments, studies in humans with memory problems diagnosed by magnetic resonance imaging showed that it was possible to visually verify hippocampal abnormality, which was found to be small and atrophied.

Thus, as astrocytes are partly responsible for the regulation and formation of synapses, in addition to modulating brain activity, Ota et al. (2013) consider that there is a high possibility of correlation between these cells playing a fundamental role in memory and learning processes, both in humans and in animals in culture, especially with regard to the hippocampus.

Other functions of astrocytes are cited as filling the spaces between neurons, regulating neurotransmitters, regulating concentrations of various substances with the potential to interfere with normal neuronal functions, supporting the brain, and participating in the blood-brain barrier, granting immunity and maintaining cerebral homeostasis.

Epilepsy is a group of brain disorders characterized by the unpredictable and periodic occurrence of seizures. The cause is unknown, but they can arise as a result of brain injuries, strokes, brain tumors, brain infections, and birth defects through a process defined as epileptogenesis.

The most common of these pathologies is hippocampal sclerosis or medial temporal sclerosis. It is characterized by gliosis, loss of neuronal cells in the hippocampus, synaptic reorganization, and microvascular proliferation. A study published in PloS Biology shows that the interaction between neurons and astrocytes is one of the mechanisms that lead to the generation of epileptic discharges. Astrocytes were once thought to be simple "helpers" of neurons, but over time, cells that play a more active role in the brain have been discovered. Astrocytes express ion channels, receptors, transmitters, and transporters and therefore have mechanisms to detect and res-

pond to neuronal activity. Glutamate transporters are located in various types of neuronal cells, but astrocytes are mainly involved in glutamate uptake (Steinhauser and Seifert, 2012).

GLT-1, a glutamate transporter located on astrocytes, is involved in the clearance of most extracellular glutamate and leads to elevated levels in epileptic foci. In addition, glutamine synthase was reduced in the hippocampus of patients with temporal lobe epilepsy compared to healthy patients. This downregulation results in a slow glutamate-glutamine cycle and accumulation of the transmitter in the extracellular space and astrocytes, providing a metabolic mechanism for astrocyte-dependent hyperexcitability. Several studies have highlighted the role of ionotropic glutamate receptors in seizures.

AMPA receptors, especially the subtype consisting of the GluR1 to GluR4 subunits, are abundantly expressed in astrocytes. Increased expression of the inverted variant GluR1 of the expanded receptor in hippocampal astrocytes of patients with epilepsy. Prolonged receptor opening increases the influx of Na+ and Ca2+ ions, blocks astrocyte Kir channels that increase depolarization, and reduces the K+ buffering capacity of astrocytes (Steinhauser and Seifert, 2012). This entire process contributes to hyperexcitability. In this case, extracellular [K+] can increase from ~3 mM to 10-12 mM; glial cells absorb most of the K+ released by active neurons. Astrocytes are also connected by gap junctions, which allow these cells to redistribute excess accumulated K+ ions through the glial network to sites of intense neuronal activity. Thus, there is growing evidence that dysfunctional astrocytes and s play a crucial role in the development of epilepsy (Steinhauser and Seifert, 2012).

Alzheimer's disease (AD) is a neurodegenerative disease with motor abnormalities, cognitive changes, and behavioral disorders. It is characterized by the accumulation of beta-amyloid plaques in the walls of blood vessels and the accumulation of tau protein in nerve cells. Astrocytes in this pathology lead to the loss of neuroprotection and the acquisition of pathological characteristics. Initially, astrocytes play a protective role in the uptake and degradation of β-amyloid. Disease progression leads to reduced clearance of beta--amyloid astrocytes, which contributes to gain of function.

In addition, β-amyloid accumulation stimulates astrocytes to produce pro-inflammatory mediators, thereby inducing positive feedback activation. Beta-amyloid has been shown to cooperate with various receptors located on astrocytes, such as scavenger receptors, TLRs, lipoproteins, glycoproteins, and acetylcholine receptors, chemokines, and complement receptors. Scavenger receptors are a group of evolutionarily conserved membrane receptors expressed on the surface of microglia, macrophages, and dendritic cells (Brandenburg et al., 2010). To date, they have been classified into six classes (receptor captors A, B, C, D, E, and F), although some members of this family remain unclassified (RAGE, CD163, and SR-PSOX). Of particular interest during AD are CD36, RAGE (receptor for advanced glycation end products), SCARA-1 (scavenger receptor for A-1), and MARCO (macrophage scavenger receptor for collagen). SCARA-1 is involved in Aβ clearance, while MARCO forms a complex with formyl peptide receptor type 1 (FPR1) upon encountering Aβ. MARCO reduces the inflammatory response of microglia via FPR-1 via intracellular ERK 1/2 signaling and cAMP inhibition (Brandenburg et al., 2010). CD36 and RAGE are associated with Aβ activation of microglia. CD36 cooperates with other innate immune pattern recognition receptors, such as TLRs, to delineate pathogen-specific responses. Once engaged by Aβ, CD36 forms

a complex with TLR-6 and TLR-4, leading to ROS production and inflammasome activation.

The RAGE receptor, one of the best-characterized unclassified scavenger receptors, has been reported to produce proinflammatory changes in astrocytes when it binds to beta-amyloid. RAGE, in turn, activates NF--κB and its downstream pathways, including p21, Cdc42-Rac, ras, MAPK, ERK, and JNK. RAGE is highly expressed in the vasculature and neurons of AD brains compared to non--diseased brains. RAGE, located on endothelial cells, has been implicated in the transport of Aβ into the brain and has also been associated with increased monocyte exudation across the blood-brain barrier.

Once bound to soluble Aβ, RAGE induces microglial activation and chemotaxis following a concentration gradient, leading to the accumulation of microglia around Aβ plaques. RAGE also mediates the phagocytic properties of astrocytes and interactions with other ligands involved in Alzheimer's disease neuroinflammation, including S100β. Astrocyte production of S100β is a common feature of Alzheimer's disease (Brandenburg et al., 2010). It is associated with depressive behavior and cognitive flexibility, and modulates neuronal oscillations. Furthermore, morphological changes in astrocytes in Alzheimer's disease involve altered neurovascular regulation of K+, leading to irregular cerebral blood flow through the downregulation of Kir4.1 and BKCa (Brandenburg et al., 2010).

Furthermore, β-amyloid accumulation alters Ca2+ signaling.In astrocytes, this accumulation alters the expression of nicotinic acetylcholine receptors (nAchRs) and metabotropic glutamate receptor 5 (mGluR5), altering Ca homeostasis. Through this pathway, astrocytes increase glutamate signaling and lead to downregulation of its transporter. Aberrant glutamate transport is associated with altered cholesterol synthesis. A prodromal symptom of Alzheimer's disease may be low glucose metabolism. Carriers of the apolipoprotein Eε4 (APOEε4) allele have lower glucose metabolism in different regions of the brain and a higher risk of AD (Brandenburg et al., 2010). Astrocyte signaling is a useful target for preventing and controlling the development of AD.

In light of the literature review presented, we move on to the final considerations, in agreement with Goergen and Cruzes (2012), who emphasize that:

> Astrocytes have several functions, still in the process of scientific elucidation, and it is accepted that there are functions that are not even known. Neuroscience and, consequently, medicine still have much to gain from discoveries about the functioning of such cells.

FINAL CONSIDERATIONS

Astrocytes, also known as astroglia, are star-shaped glial cells that are characteristic of the brain and spinal cord. They are derived from heterogeneous populations of progenitor cells in the neuroepithelium of the developing CNS. Among the many functions they perform is the biochemical control of endothelial cells, a type of flattened cell of variable thickness that lines the interior of blood vessels, which form the blood-brain barrier. They also play a role in supplying nutrients to nerve tissue, maintaining extracellular ion balance, and regulating cerebral blood flow. They play a role in repair and healing after infections and traumatic injuries. They are the main sources of cholesterol. Apolipoprotein E (apo E) is of fundamental importance in the transport of cholesterol from astrocytes to neurons and other glial cells, allowing the reconversion of lipids and the repair of brain damage.

With the development of this study, it was possible to verify that astrocytes have the func-

tions of isolating, sustaining, and nourishing neurons; are an integral and essential part of synaptic exchanges (passive homeostatic control of synaptic conditions and function), are important multifunctional regulators of neurometabolic coupling, control blood flow in the central nervous system through the release and production of vasoactive molecules, and are also primary mediators at the site of blood flow in relation to various neuronal activities of the central nervous system; They perform detoxification and phagocytosis, have immune functions, and play an essential role in the formation and maintenance of the blood-brain barrier and, consequently, in the necessary modulations in immuno-inflammatory responses. In addition, astrocytes play an important role in diseases such as Alzheimer's and epilepsy, and are important for the development and improvement of new techniques for treating these diseases.

REFERENCES

ARAQUE, Alfonso et al. **Tripartite synapses: glia, the unacknowledged partner.** 1999. Trends in neurosciences, 22(5), 208–215.

ARAQUE, Alfonso, & NAVARRETE, Marta.. **Glial cells in neuronal network function**. 2010. Philosophical Transactions of the Royal Society of London B: Biological Sciences, 365(1551), 2375–2381.

BANERJEE R, et al. **The undertow of sulfur metabolism on glutamatergic neurotransmission.** 2008. Trends Biochem Sci. 33, 413-419.

BRANDENBURG, L. O., KONRAD, M., WRUCK, C. J., KOCH, T., LUCIUS, R., PUFE, T. **Functional and physical interactions between formyl-peptide-receptors and scavenger receptor MARCO and their involvement in amyloid beta 1-42-induced signal transduction in glial cells**. 2010. J. Neurochem. 113, 749–760.

BRAMANTI, P.,et al. **Signal transduction pathways involved in protective effects of melatonin in C6 glioma cells.** 2008. J Pineal Res 44,78-87.

BELLAVER, Bruna. **O PAPEL DOS ASTRÓCITOS NO ENVELHECIMENTO CEREBRAL:** avaliação de parâmetros glutamatérgicos, oxidativos e inflamatórios em culturas hipocampais de ratos wistar. 2015. 103 f. Dissertação (Mestrado) - Curso de Ciências Biológicas-Bioquímica, Ufrgs, Porto Alegre, 2015.

BIGNAMI, A. **Discussions in Neuroscience.** 1991. Vol. 8. Elsevier Science Publishers, Amsterdam, p. 1-45.

CABEZAS R, et al. **Astrocytic modulation of blood brain barrier: perspectives on Parkinson's disease.** 2014. Front Cell Neurosci. 8, 211.

CHARLES, Andrew et al. **Intercellular signaling in glial cells: calcium waves and oscillations in response to mechanical stimulation and glutamate.** 1991. Neuron, 6(6), 983–992.

CORNELL-BELL et al. **Glutamate induces calcium waves in cultured astrocytes: long-range glial signaling**. 1990. Science, 247(4941), 470.

DANBOLT NC. **Glutamate uptake.** 2001. Prog Neurobiol. 65, 1-105.

EULENBURG V, GOMEZA J. **Neurotransmitter transporters expressed in glial cells as regulators of synapse function.** 2010. Brain Res Rev. 63, 103-112.

FABRICIUS K, et al. **Effect of age on neocortical brain cells in 90+ year old human females--a cell counting study.** 2013. Neurobiol Aging. 34, 91-99.

GARDONI F , DI LUCA M. **New targets for pharmacological intervention in the glutamatergic synapse**. 2006. Eur J Pharmacol. 545, 2-10.

GOERGEN, Diego Inacio; CRUZ, Dennis Baroni. **CONCEITOS ATUAIS SOBRE OS ASTRÓCITOS.** Salão de Ensino e de Extensão, Santa Cruz do Sul, v. 1, n. 1, p. 1-2, 22 out. 2012.

GORDON, Grant et al. **Astrocyte control of the cerebrovasculature**. 2007b. Glia, 55(12), 1214–1221.

HAYDON, Philip G. **GLIA: listening and talking to the synapse.** 2001. Nature Reviews Neuroscience, 2(3), 185–193.

IZQUIERDO I, et al. **Different molecular cascades in different sites of the brain control memory consolidation.** 2006. Trends Neurosci. 29, 496-505.

KETTENMANN, H., VERKHRATSKY, A. **Neuroglia: the 150 years after**. 2008. Trends Neurosci 31, 653-659

KOEHLER RC, et al. **Astrocytes and the regulation of cerebral blood flow.** 2009. Trends Neurosci. 32, 160-169.

MARAGAKIS NJ , ROTHSTEIN JD. **Mechanisms of Disease: astrocytes in neurodegenerative disease**. 2006. Nat Clin Pract Neurol. 2, 679-689.

Menet V, et al. **Inactivation of the glial fibrillary acidic protein gene, but not that of vimentin, improves neuronal survival and neurite growth by modifying adhesion molecule expression.** 2001. J Neurosci. 21, 6147-6158.

METEA, Monica R, & NEWMAN, Eric A. **Glial cells dilate and constrict blood vessels: a mechanism of neurovascular coupling**. 2006b. Journal of Neuroscience, 26(11), 2862–2870.

MONTGOMERY D. L. **Astrocytes: form, functions and roles in diseases.** 1994. Vet. Pathol. 31:145-167.

NEDERGAARD, M et al. **New roles for astrocytes: redefining the functional architecture of the brain**. 2003.Trends Neurosci. 26, 523-530.

OTA Y, et al. **The role of astrocytes in the regulation of synaptic plasticity and memory formation.** 2013. Neural Plast. 2013, 185463.

PEREA, Gertrudis, & ARAQUE, Alfonso. **Glial calcium signaling and neuron–glia communication.** 2005. Cell Calcium, 38(3), 375 – 382. Frontiers in calcium signalling.

PEREA, Gertrudis et al. **Tripartite synapses: astrocytes process and control synaptic information.** 2009. Trends in neurosciences, 32(8), 421–431

PIVOVAROVA NB , ANDREWS SB. **Calcium-dependent mitochondrial function and dysfunction in neurons.** 2010. FEBS J. 277, 3622-3636.

RODRIGUEZ-ARELLANO JJ, et al. **Astrocytes in physiological aging and Alzheimer's disease.** 2015. Neuroscience.

RODRIGUEZ JJ ,et al. **Complex and region-specific changes in astroglial markers in the aging brain.** 2014. Neurobiol Aging. 35, 15-23.

SAMPEDRO-PIQUERO P, et al. **Astrocytic plasticity as a possible mediator of the cognitive improvements after environmental enrichment in aged rats.** 2014. Neurobiol Learn Mem. 114, 16-25.

SEGOVIA G, et al. **Glutamatergic neurotransmission in aging: a critical perspective.** 2001. Mech Ageing Dev. 122,

SQUIRE LR, et al. **Magnetic resonance imaging of the hippocampal formation and mammillary nuclei distinguish medial temporal lobe and diencephalic amnesia.** 1990. J Neurosci. 10, 3106-3117

STEINHAUSER, C., SEIFERT, G. (2012). **Astrocyte dysfunction in epilepsy**. 2012. Jasper's Basic Mechanisms of the Epilepsies.

STOBART JL , ANDERSON CM. **Multifunctional role of astrocytes as gatekeepers of neuronal energy supply.** 2013. Front Cell Neurosci. 7, 38.

VOLTERRA, A, & BEZZI, P. **Release of transmitters from glial cells.** 2002. The Tripartite Synapse: Glia in Synaptic Transmission, 164–184.

WANG DD , BORDEY A. **The astrocyte odyssey.** 2008. Prog Neurobiol. 86, 342-367.

ZONTA, Micaela et al. **Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation.** 2003. Nature neuroscience, 6(1), 43.

ZHANG Y, PARDRIDGE WM. **Rapid transferrin efflux from brain to blood cross the bloodbrain barrier.** 2001. J Neurochem. 76, 1597-1600.