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ROLE OF ASTROCYTES IN CENTRAL NERVOUS SYSTEM, DISEASE IMPLICATIONS AND NEW PHYSIOLOGICAL IMPLICATIONS IN MEMORY AND LEARNING

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Abstract

Inside Central Nervous System (CNS) appears neurons and glia cells. There are more glial cells than neurons and have more functions than neurons. Glia name represents different kind of cells, ones from neural origin (astrocytes, radial glia, and oligodendroglia), and others from blood monocytes (microglia). During ontogeny, neurons appear first (rat fetal 15th) and after astrocytes (rat fetal 21th) indicating a bigger importance function in the CNS. Also, during the phylogeny, reptiles have less astrocytes compared to neurons and in humans, astrocytes are double in number than neurons. This data, perhaps means that astrocytes are more special cells and work in memory and learning? Astrocytes have an important role in different mechanisms protecting CNS across the production of antioxidant and anti-inflammatory proteins, cleaning extracellular medium and helping neurons to communicate with each other correctly. Inflammatory mediators production are important to prevent changes in normal physiology. But, excessive or continue production leads to many diseases, such as Alzheimer's disease (AD), Sclerosis Lateral Amyotrophic (ELA), Multiple sclerosis (MS), and neurodevelopment diseases, like Bipolar disorder, Schizophrenia, and Autism's symptomatology. Different drugs and thecniques can reverse oxidative stress and/or inflammatory excess. This review is intended to serve as an approximation to the field.

Keywords: Astrocytes; Neurons; Learning; Memory; Inflammation; Oxidative stress; Neurodegeneration; Neurodevelopment diseases; Sleep disorders.

Running Title: Astrocytes implication in CNS

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Development of the hypothesis

Neurons and glia (astrocytes, radial glia, oligodendroglia and microglia) constitute CNS (Fig. 1) [1]. Astrocytes have different populations surrounding neurons and that is true for protoplasmic astrocytes, which contact with neurons normally in the grey substance, for fibrous astrocytes that contact neuronal extensions, normally in the white substance, and also for varicose and interlaminar projections [2]. The functions performed by astrocytes are, among others, control sleep process, form the extracellular matrix, serve as a support, build, and regulate the blood-brain barrier, keep the equilibrium of extracellular ions, control production of neurotransmitters, and modulate the synaptic function between neurons and astrocytes (Tripartite Synapse Hypothesis). During the sleep period consolidation of memory occurs [3]. They can control the sleep proces by communication with other cells in the brain. They clean, during the sleep period, toxins, neurotransmitters, and liberate water, ions, and molecules.

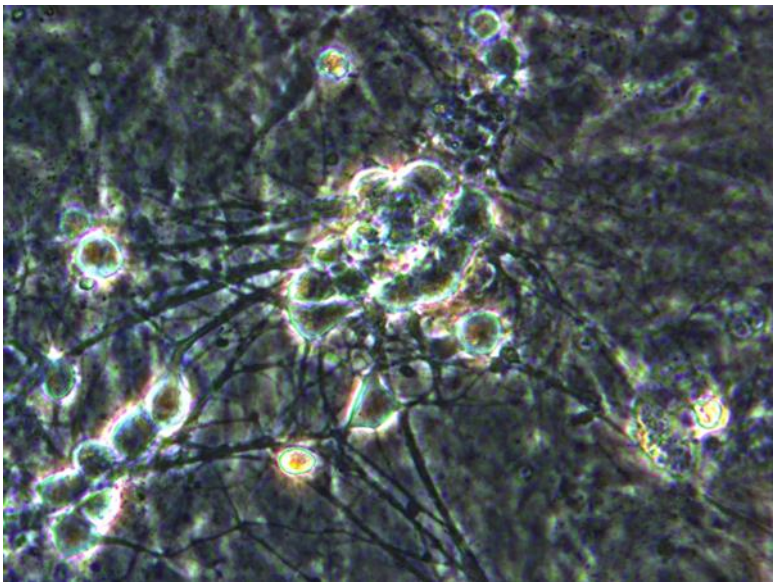

Figure 1: Neurons in primary culture (7 days). Neurons and Radial glia are detected using Phase-contrast microscope

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Many neurons are comunicating with another neurons and/or with astrocytes, remembering situations lived or dreams wanted. But, which kind of cells are working in these functions? We believe that neurons and astrocytes, are the essential elements in all these processes. Only neurons are firing cells that communicate all cells in our body. Probably astrocytes help neurons to do that, with stable communications and firing situations. This manuscript is intended to show a new idea about the role of astrocytes inside our nervous system. Many neurons are communicating with another neuron and/or with astrocytes, remembering situations lived or dreams wanted.

When we stop a computer and switch it on after two years, it continues working and only needs energy. It remembers all and how to obtain the information across its circuits. Neurons need to be active all time to remember and to firing. But astrocytes do not need it, because modulating Ca2+ variations, and perhaps using another pathways and signals, they can communicate with each other and with neurons [4]. In fact, in neurodevelopment, disorders like autism, different forms of schizophrenia, and early-onset bipolar disorder, the number and morphology of astrocytes change from one situation to another. For example, in bipolar disorder, patients noted an increase in brain functions when they are in an optimistic way and with the impossibility to record and have brain jobs when are in depress situations. The change from an optimistic to depression situation is not quickly and spends days, perhaps weeks, but is consistent. Looking at neurons, their functions cannot explain that situation, because they are cells that do all or nothing. The information is now or not. The action potential is true or false, so changes are impossible. On the contrary, astrocytes do not communicate with themselves or other cells if is not necessary, but a web

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between astrocytes exists and when it is necessary, they start a big communication between them and with neurons, oligodendroglia, and microglia. Future hypothesis looking for the role of astrocytes in mammalian functions will be necessary and a new field in the astrocytes job in the nervous system has been opened now. That will provide a new direction for future interventions in CNS diseases.

Astrocytes respond to changes in their microenvironment because they have two types of processes. Perisynaptic processes, with fine extensions to the interneuronal synapse and vascular processes with final lengthenings (endfeet) communicating with blood vessels. Perisynaptic processes express receptors for neurotransmitters, cytokines, chemokines, growth factors, and ion channels. Furthermore, transporters and receptors for glutamate, so controlling neuronal glutamatergic neurotransmission [5,6]. The endfeet in astrocytes express glucose transporters and aquaporins 4 and covers most of the blood vessels [6]. Moreover, astrocytes are territorial cells with processes controlling territory with only a few overlap between neighboring astrocytes [7] which are interconnected into functional networks [8,9]. It has been demonstrated that astrocyte cell contact with up to 2,000,000 synapses [4,10] and this interaction depends on changes in neuronal activity. Thanks to that astrocytes offer energy to neurons by lactate shuttle [11,12] and modulate Ca2+ variations [13]. Respecto to gender differences, data from rodents demonstrated significant differences in glia between males and females [14,15]. Testosterone is produced by the testis of male change to estradiol in the brain. In the male preoptic area, astrocytes are more ramified with more density of dendritic spines. Also, have a higher density of microglia with reduced branching pattern. In neurodevelopment, disorders like

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autism, different forms of schizophrenia, and early-onset bipolar disorder, males are at higher risk than females to develop these disorders and have been published the role of glia in all of them. Autism is four to eight times more common in males [16,17] with hypermasculinized phenotypes [18] (Fig. 2).

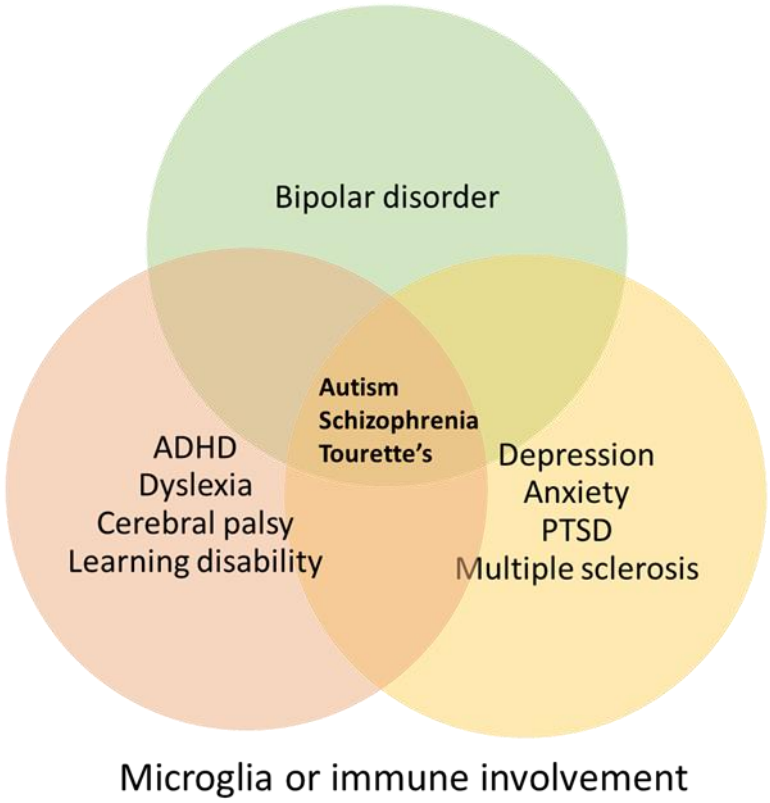

Figure 2: Disorders with microglia or immune involvement. Different illness and their relationship

Astrocytes change after inflammation or injury, becoming reactive. In this case, there are two types of astrocytes, hypertrophic, and those that form scars [19]. The changes affect different pathologies such as Alzheimer's disease, Huntington's disease, ischemic stroke, and epilepsy. In Alzheimer's disease (AD) and multiple sclerosis (MC) reduction in brain weitht is detected, with increase in grooves and a loose of water in general. During the day, astrocytic cells are swollen with fluid that they pour out at night cleaning the brain from toxins,

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proteins, and unwanted molecules. When astrocytes are damaged (Fig. 3), during the waking period, cannot return water inside, losing the possibility to clean toxins at the following night and increasing the presence of toxins.

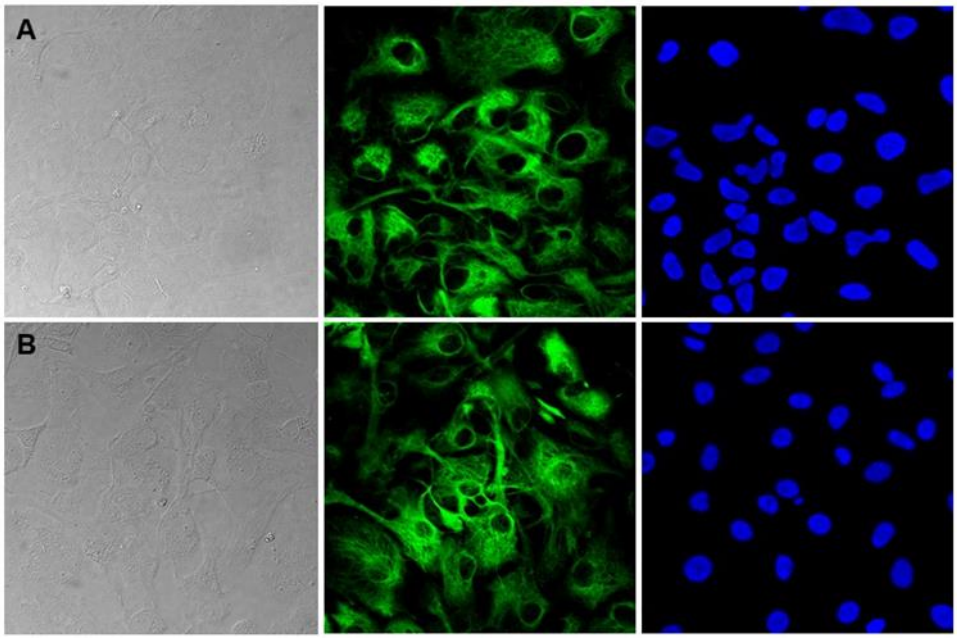

Figure 3: Astrocytes in primary culture $A\beta_{1-42}$ (A) or $A\beta_{1-42}$ (B). 6 h with 5 μM $A\beta_{40-1}$ (control) or $A\beta_{1-42}$ (Aβ). $A\beta_{1-42}$ increases mitochondrial aggregation in astrocytes in primary culture. Confocal microscopy: Mitotracker (250 nM) to stain mitochondria and Hoechst 33342 (2 μg/ml) to stain nuclei.

Astrocytes give glutamine to neurons and eliminate glutathione from the synapsis. In AD, neurons die because hyper-phosphorylation of TAU (π protein) occurs. Probably astrocytes are involved in this process because reduction of glutamine to neurons or/and elimination of glutathione will not occur. Furthermore could be a reduction in ATP, produced by mitochondria damaged [3]. Inside the brain, oxygen is necessary and cross from circulatory system to extracellular space between brain cells. If circulation, with the good function of the heart, does not produce, oxygen will be going down and brain cells could have problems to produce adenosine triphosphate (ATP) and transport messenger from neuron

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body to synapse. So, cardiology specialists, neurologists, psychologists, and medical specialists in the developing brain will be in contact from now to the future [19]. On the other hand, astrocytes are involved in non-physiological pain [20]. Communication between the cells of the sensory ganglia could be important in the treatment of chronic pain [21,22] (Fig.4).

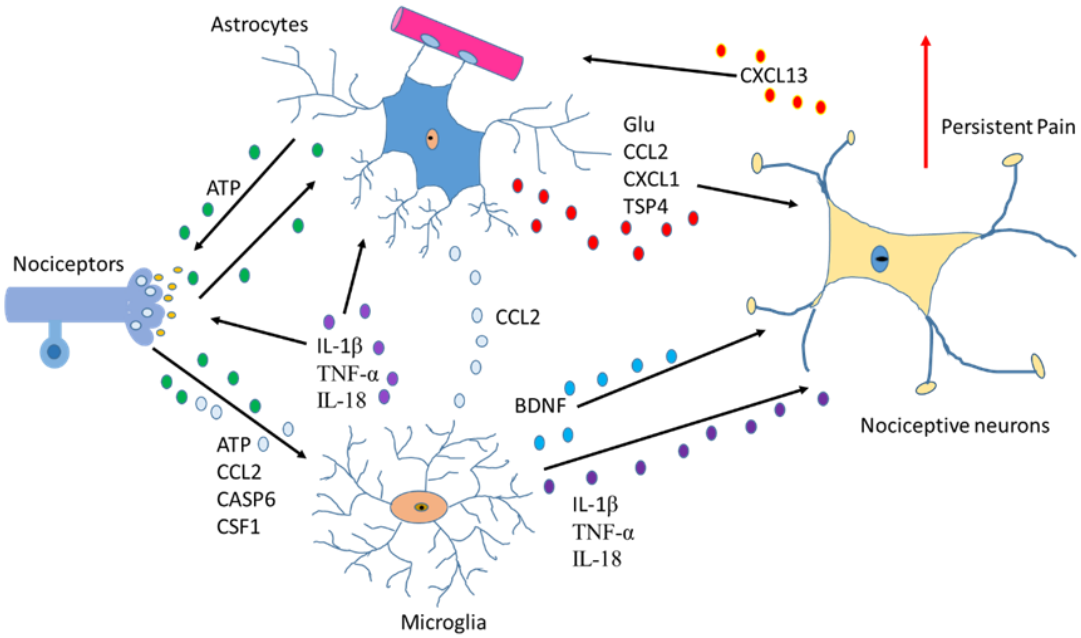

Figure 4: Communication between astrocytes, neurons and microglia in pain situations.

Activation of nociceptors causes the induction of cytokines, chemokines, BDNF and neurotrophic factors producing changes an increase of persistent pain.

Astrocytes and inflammation

Analogously to microglia, the role of astrocytes in inflammation has been studied. During cerebral ischemia, these cells act as protectors. On the contrary, against lipopolysaccharide-mediated inflammation (LPS), they appear to be detrimental. However, in the cells of the retina, it has been demonstrated an anti-inflammatory

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and neuroprotective effect through the production of lipoxins, against acute and chronic lesions [23]. Furthermore, the cytokine IL-33 produced by astrocytes has an essential role in the development of neuronal circuits [24]. Other studies showed that the activation of certain transcription factors are involved in producing protective (STAT3) [25] or injurious effects (NF-κB) [26]. Moreover, there is also a correlation between IL-1α and the greater number of GFAP-immunoreactive astrocytes [27]. On the other hand, in multiple sclerosis, TNF-α alters synaptic transmission affecting the cognitive level [28].

Inflammatory signals are present in the mild cognition impairment (MCI) patient before they develop AD [29]. Inflammation is a crucial factor in AD progression as is seen in activating microglia and increasing reactive astrocytes in these patients. Astrocytes can change their shape during hypertrophy and increase their ramifications, moving to the injury site [30]. Patients with AD present reactive astrocytes as detected by PET (Positron Emission Tomography) imaging [31,32] and also, before the formation of plaques in APP transgenic mice [33].

In reactive astrocytes, the level of gliotransmitters (including glutamate, ATP, d-serine and GABA) can produce inhibition of neuronal activity [34]. In amyloid plaques, an increase in GABA protein has been detected in reactive astrocytes which surround the plaques and that trigger more release into the extracellular space [34,35]. There is a consensus that the role of GABA, is protecting neural cells in the brain [35]. Furthermore, Delekate's group showed that astrocytes in APP/PS1 mice (Mice carrying the human Swedish amyloid precursor protein and the Δe9 presenilin 1 mutation) increase the release of ATP surrounding the plaques. This happens because the Ca2+ concentration rises inside the cell [36]. The latter gives us the idea that an increase in ATP in astrocytes and neurons

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could help to reduce the neuronal death that occurs in Alzheimer's. The increase in the production of ATP by the mitochondria could help to recover from AD and decrease the development of the illness. The use of a cold laser could elevate ATP produced by mitochondria due it can act on cytochrome c oxidase, increasing energy in the cells. This could help mild cognitive impairment patients before they develop to AD [19]. Obviously, in AD patients the use of the laser could be unproductive in the majority of cases because the cells are already dying. MS is a CNS (Central Nervous System) disorder characterized to be a chronic inflammatory autoimmune disease. Both environmental and genetic factors [37] are involved and patients development three states: 1) presenting a relapsing-remitting clinical course, characterized by episodes of acute neurological dysfunctions followed by periods of recovery [38] (20-30% of patients). 2) Progression to a chronic secondary clinical-stage is characterized by a worsening with increased disability (50% of patients) [39]. 3) In the 15% of patients, MS progress to the clinical gradual decline in neurological functions [40]. In animal models of MS disease show that it is an autoimmune inflammatory disorder because of the recruitment of reactive lymphocytes, CD4+ T cells (Cluster of Quadruple Differentiation in T cells and the dendritic cells). Focusing on the three states, it seems that in the first state the bipolar relapsing and remitting states look like the illness produced by the virus chikungunya (CHIK) [41], or the plasmodium (as malaria) or bacterial infection, with high and low episodes of affectation. The bipolar action will be related to the immune cells and their role controlling the damage in the different diseases.

The gliotransmitter, glutamate, is released by astrocytes when the amyloid-beta is detected in the medium and provokes neural spine loss and synaptic damage

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by activation of NMDA (N-Methyl-D-Aspartate) receptors [42]. Also, astrocytes release purines that can influence the development of AD or other illness and activate the production of inflammatory proteins, decreasing anti-inflammatory proteins [43]. Furthermore, in APP/PS1 mice of 7 month age, an increase in chemokines and its receptors compared with the wild type mice has been detected [44], showing the role of cytokines and chemokines from microglia and astrocytes in APP/PS1 mice [43]. Moreover, this group detected, for the first time, changes in CCR5 (Chemokine (C-C motif) Receptor 5) and CCR8 (Chemokine (C-C motif) Receptor 8) expression in these mice with high production of amyloid β. These results demonstrate that changes in inflammatory protein expressions could affect neurodegeneration, development of the brain and also cognition and memory [43,44]. Also, using lipopolysaccharide (LPS) as an inductor, astrocytes increase the expression of many genes of the complement cascade [45]. On the other hand, the upregulation of trophic factors after ischemic damage has been shown to have a protective mechanism. But the role of astrocytes could be different depending on age and the situation of these cells in our body (Fig. 5) and probably not only two states of astrocytes exist.

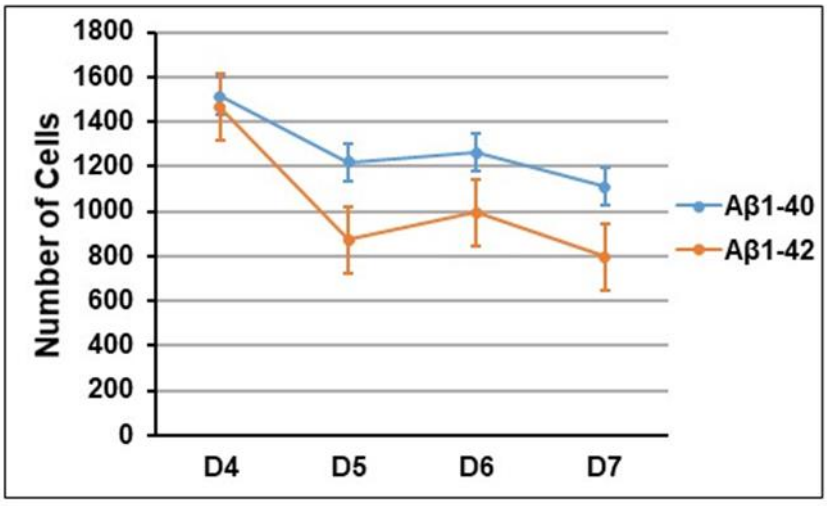

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Figure 5: Live cells attached to the plaque. A number of astrocytes in primary culture with or without $A\beta_{1-42}$. D4,5,6,7 (day of culture). Aβ was added the 4th day of culture.

Astrocytes and oxidative stress

Free radicals are pro-oxidant molecules containing one or more unpaired electrons. Depending on the molecules they come from oxygen, nitrogen, lipids, etc. Furthermore, they can take electrons from other molecules making them highly reactive [46].

The increase of ROS (Reactive Oxygen Species) levels are related to many neurodegenerative diseases [47,48], and furthermore, effects of antioxidants in clinical studies have been highly disappointing, due to that the high concentration of antioxidants acts in many cases as a prooxidant [49], or because oxidative stress occurs relatively early in the course of diseases, and/or the combination of the antioxidants falls in a clinic situation [50]. Activated immune cells can produce ROS contribute to mitochondrial dysfunction and neural cells death by apoptosis (Fig. 6). Superoxide dismutase (SOD) converts free superoxide radicals to molecular oxygen and hydrogen peroxide, which is broken by the catalase enzyme [51,52].

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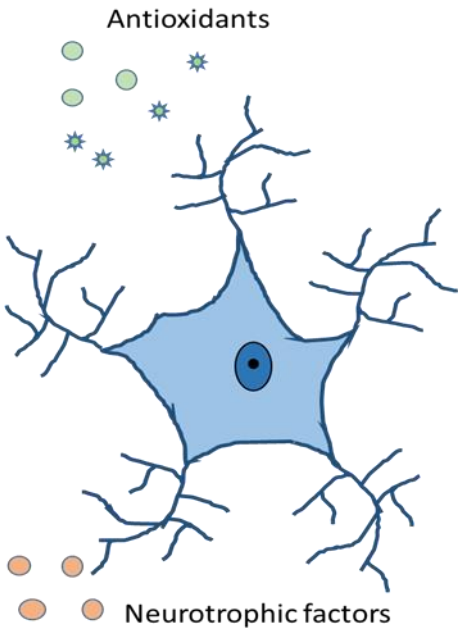

Figure 6: Healthy physiological astrocytes. Release of neurotrophic factors and antioxidants, ion homeostasis, detoxification of ROS/RNS, fluid transport, vasodilation and neurotransmitter reuptake.

Microglial cells are the main immune cells in the CNS and the role of oxidative stress has been well studied in this cell type. In contrast, the role that astrocytes play is scarce.

Astrocytes protect neurons front oxidative stress, producing antioxidant proteins [53]. The amyloid-beta toxic peptide causes hydrogen peroxide production by astrocytes [54], as we have indicated before [48], and they release ROS in response to amyloid-beta via the pentose-phosphate pathway. Drugs that can protect astrocytes and neurons from inflammation and/or oxidative stress damage have been used in AD cells in culture, in animal models and in humans [44,55,56], but neither of them cannot obtain a recovery and/or a less development of the AD. Moreover, we have the same situation for other illnesses (Fig. 7).

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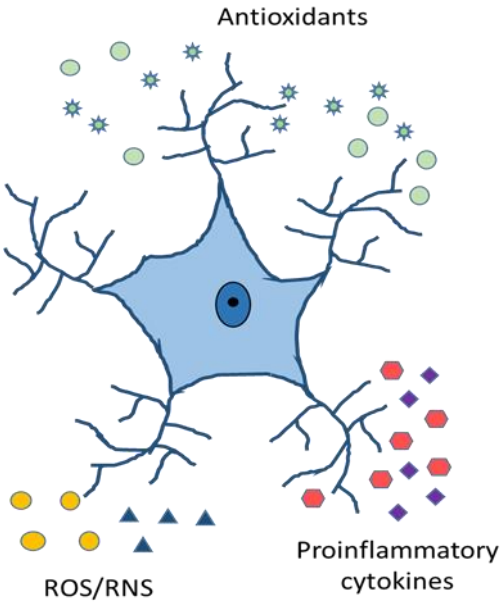

Figure 7: Reactive astrocytes. Release cytokines and chemokines, ROS/RNS production, increased expression of GFAP, vimentin and Glu, compensatory release of antioxidants

Due to the high metabolic rate of the neurons, these cells produce more free radicals than other cells of the nervous system. Neurons also have a reduced ability to eliminate reactive oxygen species, which makes them highly vulnerable to oxidative stress [57]. In many neurodegenerative disorders have been detected an increase of free radicals that can induce aggregations of proteins and it happens in many diseases, such as PD, AD, ALS, HD, etc. [58-61]. In sporadic cases of Alzheimer's disease, age factors are important and can influence the Aβ-amyloid processing by losing mitochondrial function and excessive ROS production [62]. Alternatively, α-synuclein aggregates caused by dopaminergic neurons in Parkinson's disease disrupts mitochondrial function and then producing oxidative stress [63,64]. Moreover, α-synuclein aggregation can be produced by an increase in oxidative stress [65]. One form of amyotrophic lateral sclerosis (ALS) caused by superoxide dismutase 1 (SOD1) mutation [66],

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presents the affectation of the antioxidant molecules balance with the increase in oxidative stress [67], due to aggregation of SOD 1 [68]. The diseases indicated above and together with HD share aggregation process and oxidative stress that together produce a vicious cycle [69].

Neurodegeneration Mechanisms

In the neurodegenerative cascade, several basic mechanisms can intervene, such as apoptosis, necrosis, autophagy, retrograde neurodegeneration, Wallerian degeneration, demyelination and astrogliopathy [70]. There is evidence of apoptotic mechanisms in animal models of various neurodegenerative diseases, but the evidence in human tissues is limited. The activation of caspase-1, -3, -8 and -9 and the release of cytochrome c observed in models of Huntington's disease (HD) is demonstrated in human striated brain tissue [71,72]. Similarly, caspases activation and neuronal apoptosis have been detected in ALS [73] and HIV [74]. In necrosis, non-caspases-dependent death, act two major effector proteins serine / threonine-protein kinase 1 (RIPK1) and the mixed lineage kinase domain (MLKL). In murine ALS models have been detected the release of TNF-α, FasL and TRAIL by astrocytes, that can trigger necrosis through the activation of RIPK1 and MLKL [75]. Furthermore, in humans with ALS, a normal pathology mediated by RIPK1 has been detected [76]. On the other hand, in MS necrotic mechanisms are also observed in pathological samples [77].

Apathy has multifactorial symptoms, as behavioural, cognitive, and emotional facets including impaired motivation and reduced goal-directed behaviour. Apathy belongs to schizophrenia, bipolar disorders and autism's negative symptomatology. The molecular mechanisms are still poorly studied [78,79].

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Correlations between apathy with specific brain regions and executive functions have been shown (the anterior cingulate cortex, orbitofrontal cortex and the ventral and dorsal striatum). It is considered the major neuropsychiatric symptom in both acquired and neurodegenerative disorders such as strokes [80], AD [81], ELA [82] or Parkinson's disease [83]. All these disorders have a disturbance of the normal balance of neurotransmitters and are associated with anomalies in specific brain regions and inflammatory pathways leading to glia activation and finally neuronal and neural loss [84]. In MS there is a decomposition of the blood-brain barrier (BBB), death without regeneration of oligodendrocytes, loss of myelin, axonal degeneration and reactive gliosis of astrocytes and activation of microglia [85,86]. In the disease, inflammation plays an important role with an increase in cytokines and chemokines. In the pathophysiology of MS, the BBB is compromised, causing activation of the microglia and the immune cells of the periphery. The microglia not only produces pro-inflammatory cytokine and chemokine secretion with decreased anti-inflammatory agents but also releases reactive oxygen and glutamate species [87]. Each type of cell of the innate and adaptive immune system can organize the inflammatory response within the CNS and also, the autoreactive CD4 + T cells make an important contribution in the MS.

Astrocytes, Sleep Process and Diseases

One century ago Santiago Ramón y Cajal proposed astrocytes as cells that regulate the process of sleep [3]. He detected large processes into the synapses during sleep and retraction of them during wakefulness. In 2009, the Scientifics started to be interested in the dream and the role of astrocytes in it and they detected influences of astrocytes in the sleep/wake circle [88] and then,

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astrocytes were postulated as modulator members of the homeostasis of the sleep [89]. Astrocytes release adenosine that units to its receptor, adenosine A1 receptor, occasioning sleep and driving to total sleep [89]. Furthermore, it is known that astrocytes clean the brain during sleep situations, releasing solutes and water inside the brain cleaning it through astrocytic aquaporins 4. Furthermore, in “in vivo” microdialysis studies have shown that amyloid β (the toxic peptide in Alzheimer’s brain) increases inside the interstitial fluid during wakefulness and declined during the sleep process [90], but the declination is less in Alzheimer's patients with a drop in the cleaning brain process occurs during the sleep period, produced by astrocytes [91,92]. Moreover, the changes observed in the toxic peptide diminish during AD development [93]. So, the glymphatic pathway detect could be affected in neurodegenerative patients and others, such as bipolar disorders, chronic fatigue syndrome, MS and schizophrenic situations [94]. Furthermore, the sleep/wake cycle, modulated by astrocytes, is also altered in that diseases [95,96]. Under experience in humans, many people with suffering from these diseases present an alteration REM (Rapid Eye Movement) process during the sleep period. These data could indicate alterations in the sleep period with the affectation of the active zone of the brain that initiates the switch off the brain. In fact, the patients cannot sleep well and they fill tired during the awake period, with problems in attention, memory, spatial recognition, and so on.

Therapeutic Effects to Combat Diseases

Future therapeutics against brain diseases will develop specific drugs against reactive astrocytes and microglia activation. Study on the mechanisms that eliminate amyloid beta toxic peptide, the decrement of the phosphorylation of

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TAU inside the neurons, the ATP changes in the brain controlled by astrocytes and the production of metabolites, will be necessary for finding therapeutic targets in AD and in other diseases [97].

In chronic pain, drugs controlling the mechanisms of SG cells and the interaction of these cells with the neuronal body will be important to assume the relationship between astrocytes and the other cells in the sensorial ganglia and the treatment of chronic pain.

With problems in the sleep/awake cycle, we can understand the relationship between all the CNS cells. In the future, to obtain better health, brain changes in the sleep inductor proteins and the sleep/awake cycle could help to fight sleep illness. Also, the influence of astrocytes in the brain clean process will be a therapeutic approach to eliminate toxic elements detected in many illnesses, such as Aβ in Alzheimer's, Parkinson, or ELA (Sclerosis Lateral Amyotrophic) disease and many other neurodegenerative diseases in which toxic proteins are present. Moreover, altered miRNA expression profile in ALS and/or other neurodegenerative disease patients has been detected with an increase of inflammation produced by microglia and astrocytes reactivities, which there are potential mediators of neurodegenerative processes [98,99].

Promoting toxics proteins cleaning by astrocytes (as amyloid-beta) will be necessary by different mechanisms such as autophagy or ubiquitin systems. Furthermore, in reactive astrocytes, an increase in antioxidant proteins, such as Nrf2 (Nuclear Factor Erythroid 2-related factor 2), could produce benefits for our brain. On the other hand, astrocytes can take off toxic peptides from the brain leading to reactive astrocytes and increasing, inflammation, toxic proteins and oxidative stress molecules. Regulation of oxidative stress status and

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inflammation could help neurons located near astrocytes to survey. Moreover, astrocytes can increase GABA levels after damage, so controlling MAO-B (Monoamine Oxidase-B) activity could help to rescue the brain from memory impairments, such as have been found in AD. Cerebral blood flow (CBF) declines with age. From 20 to 60 years old, CBF dips about 16% and continues to drop 0.4% every year. Reducción of oxygen and glucose delivery to the brain occurs, and this CBF dip reduce ATP energy production. Mitochondrial loss or damage with the ATP reduction worsens when vascular risk factors (VRF) to Alzheimer's disease develop and can accelerate the decline CBF and mitochondrial deficiency where mild cognitive impairment (MCI) appears (19). A form of photo bio modulation, the transcranial infrared brain stimulation (TIBS), are planned in a randomized, placebo-controlled study of MCI patients to be done at our University. The photo bio modulation has been used in Parkinson's disease, depression, traumatic brain injury, and stroke with reported benefits. Medical interventions, pharmacological approach, and so on, have been used in AD, but the TIBS will be a good new technique for the future.

Conclusion

Control of all mechanisms and the understanding of the relationship between astrocytes, neurons, oligodendroglia and microglia could become the therapeutic track to some neurodegenerative disorders and also to diseases such as bipolar disorder, schizophrenia, and autistic spectrum. Thus, different strategies can be considered to bridge the gap between human disorders and astrocytes and glia intervention. Furthermore, the presence of different types of astrocytes and increases or decreases of them depending on the diseases and age should be a predominant study in the future. Hypothesis looking for the role of astrocytes in

mammalian functions will be necessary and a new field in the astrocytes job in the nervous system has been opened now. That will provide a new direction for future interventions in CNS diseases.

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Authors' contributions

AJ designed the review, critically revised the manuscript, and corrected English in the manuscript. SKS corrected English in the manuscript. IC did experiments and interpreted the data. SLV conceived of and designed the review, drafted the manuscript and performed proofreading. All authors read and approved the final manuscript.

Conflicts of interest

All participants provided written informed consent. Participants have declared that no competing interest exists.

Ethical approval and consent to participate

All animal procedures were carried out in accordance with the European legislation on the use and care of laboratory animals (CEE 86/609). Experimental research on mice was performed with the approval of the ethics committee on animal research of the University of Valencia (Spain). All procedures were

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performed in accordance with the 1964 Helsinki declaration and its later amendments

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Bibliography

1.- Taverna, E.; Götz, M.; Huttner, W. B. The cell biology of neurogenesis: toward an understanding of the development and evolution of the neocortex. Annu. Rev. Cell Dev. Biol. 2014, 30, 465–502. doi:10.1146/annurev-cellbio-101011-155801

2.- Vasile. F.; Dossi, E.; Rouach, N. Human astrocytes: structure and functions in the healthy brain. Brain Struct. Funct. 2017, 2017222, 2017–2029. doi:10.1007/s00429-017-1383-5

3.- Araque, A.; Carmignoto, G.; Haydon, P. G. Dynamic signaling between astrocytes and neurons. Annual review of physiology 2001, 63, 795–813. doi:org/10.1146/annurev.physiol.63.1.795

4.- Corkrum, M.; Covelo, A.; Lines, J.; Bellocchio, L.; Pisansky, M.; Loke, K.; Quintana, R.; Rothwell, P. E.; Lujan, R.; Marsicano, G.; et al. Dopamine-Evoked Synaptic Regulation in the Nucleus Accumbens Requires Astrocyte Activity. Neuron 2020, 105(6), 1036–1047.e5. doi:org/10.1016/j.neuron.2019.12.026.

5.- Bélanger, M.; Allaman, I.; Magistretti, P.J. Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. Cell Metab. 2011, 14(6), 724-738. doi:10.1016/j.cmet.2011.08.016.

6.- Iadecola, C.; Nedergaard, M. Glial regulation of the cerebral microvasculature. Nat Neurosci. 2007, 10(11), 1369-1376. doi:10.1038/nn2003

7.- Kacem, K.; Lacombe, P.; Seylaz, J.; Bonvento, G. Structural organization of the perivascular astrocyte endfeet and their relationship with the endothelial glucose transporter: a confocal microscopy study. Glia 1998, 23(1), 1-10.

8.- Oberheim. N.A.; Takano. T.; Han, X. et al. Uniquely hominid features of adult human astrocytes. J Neurosci 2009, 29(10), 3276-3287. doi:10.1523/JNEUROSCI.4707-08.2009

9.- Bélanger, M.; Allaman, I.; Magistretti, P.J. Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. Cell Metab 2011, 14(6), 724-738. doi:10.1016/j.cmet.2011.08.016

10.- Oberheim, N.A.; Wang, X.; Goldman, S.; Nedergaard, M. Astrocytic complexity distinguishes the human brain. Trends Neurosci 2006, 29(10), 547-553. doi:10.1016/j.tins.2006.08.004

11.- Brooks, G.A. The Science and Translation of Lactate Shuttle Theory. Cell Metab. 2018, 27(4):757-785. doi:10.1016/j.cmet.2018.03.008

12.- Hurley, J.B.; Lindsay, K.J.; Du, J. Glucose, lactate, and shuttling of metabolites in vertebrate retinas. J Neurosci Res. 2015, 93(7):1079-1092. doi:10.1002/jnr.23583

13.- Peteri, U.K.; Niukkanen M, Castrén ML. Astrocytes in Neuropathologies Affecting the Frontal Cortex. Front Cell Neurosci. 2019;13:44. Published 2019 Feb 12. doi:10.3389/fncel.2019.00044

14.- Habib, P.; Beyer, C. Regulation of brain microglia by female gonadal steroids. J. Steroid Biochem. Mol. Biol. 2015, 146, 3–14.

15.- Lenz, K.M.; McCarthy, M.M. A starring role for microglia in brain sex differences. Neuroscientist 2015, 21, 306–21

16.- Baron-Cohen, S. Autism: the empathizing-systemizing (E-S) theory. Ann N Y Acad Sci 2009,1156, 68-80. doi:10.1111/j.1749-6632.2009.04467.x

17.- Fombonne, E. Epidemiological trends in rates of autism. Mol Psychiatry 2002, 7 Suppl 2:S4-S6. doi:10.1038/sj.mp.4001162

18.- Khakh, B.S.; Beaumont, V.; Cachope, R.; Munoz-Sanjuan, I.; Goldman, S.A..; Grantyn, R. Unravelling and Exploiting Astrocyte Dysfunction in Huntington's Disease. Trends Neurosci. 2017, 40(7):422-437. doi:10.1016/j.tins.2017.05.002

19.- de la Torre, J. C.; Olmo, A. D.; Valles, S. Can mild cognitive impairment be stabilized by showering brain mitochondria with laser photons?. Neuropharmacology 2019, 107841, Advance online publication. doi.org/10.1016/j.neuropharm.2019.107841

20.- Costa. F.A.; Moreira Neto,. F.L. Células gliais satélite de gânglios sensitivos: o seu papel na dor [Satellite glial cells in sensory ganglia: its role in pain]. Rev Bras Anestesiol 2015, 65(1), 73-81. doi:10.1016/j.bjan.2013.07.013

21.- Ledda, M.; Blum, E.; De Palo, S.; Hanani, M. Augmentation in gap junction-mediated cell coupling in dorsal root ganglia following sciatic nerve neuritis in the mouse. Neuroscience 2009, 164(4), 1538–1545. doi.org/10.1016/j.neuroscience.2009.09.038

22.- Uta, D.; Kato, G.; Doi, A.; Andoh, T.; Kume, T.;Yoshimura, M.; Koga, K. Animal models of chronic pain increase spontaneous glutamatergic transmission in adult rat spinal dorsal horn in vitro and in vivo. Biochemical and biophysical research communications 2019, 512(2), 352–359. doi.org/10.1016/j.bbrc.2019.03.051

23.- Livne-Bar, I.; Wei, J.; Liu, H.H.; Alqawlaq, S.; Won, G.J.; Tuccitto, A. et al. Astrocytederived lipoxins A4 and B4 promote neuroprotection from acute and chronic injury. The Journal of Clinical Investigation. 2017, 127(12), 4403-4414

24.- Vainchtein, I.D.; Chin, G.; Cho, F.S.; Kelley, K.W.; Miller, J.G.; Chien, E.C. et al. Astrocyte-derived interleukin-33 promotes microglial synapse engulfment and neural circuit development. Science. 2018. 359(6381), 1269-1273

25.- Anderson, M.A.; Burda. J.E.; Ren. Y.; Ao, Y.; O'Shea, T.M.; Kawaguchi, R. et al. Astrocyte scar formation aids central nervous system axon regeneration. Nature. 2016, 532(7598), 195-200

26.- Liddelow, S..A.; Barres, B.A. Reactive astrocytes: Production, function, and therapeutic potential. Immunity. 2017, 46(6), 957-967

27.- Sheng, J.G.; Mrak, R.E.; Griffin, W.S.T. Microglial interleukin-I-alpha expression in brain regions in Alzheimer's disease—Correlation with neuritic plaque distribution. Neuropathology and Applied Neurobi

28.- Habbas, S.; Santello, M.; Becker, D.; Stubbe, H.; Zappia, G.; Liaudet, N. et al. Neuroinflammatory TNFalpha impairs memory via astrocyte signaling. Cell. 2015, 163(7), 1730-1741

29.- Obrenovich, M. E.; Smith, M. A.; Siedlak, S. L.; Chen, S. G.; de la Torre, J. C.; Perry, G.; Aliev, G. Overexpression of GRK2 in Alzheimer disease and in a chronic hypoperfusion rat model is an early marker of brain mitochondrial lesions. Neurotoxicity research 2006, 10(1), 43–56. doi.org/10.1007/BF03033333

30.- Bardehle, S.; Krüger, M.; Buggenthin, F.; Schwausch, J.; Ninkovic, J.; Clevers, H.; Snippert, H. J.; Theis, F. J.; Meyer-Luehmann, M.; Bechmann, I.; et

al. Live imaging of astrocyte responses to acute injury reveals selective juxtavascular proliferation. Nature neuroscience 2013, 16(5), 580–586. doi.org/10.1038/nn.3371

31.- Carter, S. F.; Herholz, K.; Rosa-Neto, P.; Pellerin, L.; Nordberg, A.; Zimmer, E. R. Astrocyte Biomarkers in Alzheimer's Disease. Trends in molecular medicine 2019, 25(2), 77–95. doi.org/10.1016/j.molmed.2018.11.006

32.- Edison, P.; Brooks, D. J. Role of Neuroinflammation in the Trajectory of Alzheimer's Disease and in vivo Quantification Using PET. Journal of Alzheimer's disease : JAD 2018, 64(s1), S339–S351. doi.org/10.3233/JAD-179929

33.- Heneka, M. T.; Kummer, M. P.; Stutz, A.; Delekate, A.; Schwartz, S.; Vieira-Saecker, A.; Griep, A.; Axt, D.; Remus, A.; Tzeng, T. C.; et al. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. Nature 2013, 493(7434), 674–678. doi.org/10.1038/nature11729

34.- Jo, S.; Yarishkin, O.; Hwang, Y. J.; Chun, Y. E.; Park, M.; Woo, D. H.; Bae, J. Y.; Kim, T.; Lee, J.; Chun, H.; et al. GABA from reactive astrocytes impairs memory in mouse models of Alzheimer's disease. Nature medicine 2014, 20(8), 886–896. doi.org/10.1038/nm.3639

35.- Chun, H.; An, H.; Lim, J.; Woo, J.; Lee, J.; Ryu, H.; & Lee, C. J. Astrocytic proBDNF and Tonic GABA Distinguish Active versus Reactive Astrocytes in Hippocampus. Experimental neurobiology 2018, 27(3), 155–170. doi.org/10.5607/en.2018.27.3.155

36.- Delekate, A.; Füchtemeier, M.; Schumacher, T.; Ulbrich, C.; Foddis, M.; Petzold, G. C. Metabotropic P2Y1 receptor signalling mediates astrocytic

hyperactivity in vivo in an Alzheimer's disease mouse model. Nature communications 2014, 5, 5422. doi.org/10.1038/ncomms6422

37.- Thompson, A. J.; Banwell, B. L.; Barkhof, F.; Carroll, W. M.; Coetzee, T.; Comi, G.; Correale, J.; Fazekas, F.; Filippi, M.; Freedman, M. S.; et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. The Lancet. Neurology 2018, 17(2), 162–173. doi.org/10.1016/S1474-4422(17)30470-2

38.- Brownlee, W. J.; Hardy, T. A.; Fazekas, F.; Miller, D. H. Diagnosis of multiple sclerosis: progress and challenges. Lancet (London, England) 2017, 389(10076), 1336–1346. doi.org/10.1016/S0140-6736(16)30959-X

39.- Lorscheider, J.; Buzzard, K.; Jokubaitis, V.; Spelman, T.; Havrdova, E.; Horakova, D.; Trojano, M.; Izquierdo, G.; Girard, M.; Duquette, P.; et al. MSBase Study Group Defining secondary progressive multiple sclerosis. Brain : a journal of neurology 2016, 139(Pt 9), 2395–2405. doi.org/10.1093/brain/aww173

40.- Lassmann, H.; van Horssen, J.; Mahad, D. Progressive multiple sclerosis: pathology and pathogenesis. Nature reviews. Neurology 2012, 8(11), 647–656. doi.org/10.1038/nrneurol.2012.168

41.- Vu, D. M.; Jungkind, D.; Angelle Desiree LaBeaud. Chikungunya Virus. Clinics in laboratory medicine 2017, 37(2), 371–382. doi.org/10.1016/j.cll.2017.01.008

42.- Talantova, M.; Sanz-Blasco, S.; Zhang, X.; Xia, P.; Akhtar, M. W.; Okamoto, S.; Dziewczapolski, G.; Nakamura, T.; Cao, G.; Pratt, A. E.; et al. Aβ induces astrocytic glutamate release, extrasynaptic NMDA receptor activation, and synaptic loss. Proceedings of the National Academy of Sciences of the United

States of America 2013, 110(27), E2518–E2527. doi.org/10.1073/pnas.1306832110

43.- Jorda, A.; Cauli, O.; Santonja, J. M.; Aldasoro, M.; Aldasoro, C.; Obrador, E.; Vila, J. M.; Mauricio, M. D.; Iradi, A.; Guerra-Ojeda, S.; et al. Changes in Chemokines and Chemokine Receptors Expression in a Mouse Model of Alzheimer's Disease. International journal of biological sciences 2019, 15(2), 453–463. doi.org/10.7150/ijbs.26703

44.- Valles, S. L.; Iradi, A.; Aldasoro, M.; Vila, J. M.; Aldasoro, C.; de la Torre, J.; Campos-Campos, J.; Jorda, A. Function of Glia in Aging and the Brain Diseases. International journal of medical sciences 2019, 16(11), 1473–1479. doi.org/10.7150/ijms.37769

45.- Blanco, A. M.; Vallés, S. L.; Pascual, M.; Guerri, C. Involvement of TLR4/type I IL-1 receptor signaling in the induction of inflammatory mediators and cell death induced by ethanol in cultured astrocytes. Journal of immunology (Baltimore, Md. 1950), 2005, 175(10), 6893–6899. doi.org/10.4049/jimmunol.175.10.6893

46.- Beckman, J.S.; Koppenol, W.H. Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly. American Journal of Physiology-Cell Physiology 1996, 271, C1424–C1437 doi:10.1152/ajpcell.1996.271.5.C1424

47.- Islam, M. T. Oxidative stress and mitochondrial dysfunction-linked neurodegenerative disorders. Neurological research 2017, 39(1), 73–82. doi.org/10.1080/01616412.2016.1251711

48.- Markesbery, W. R.; Carney, J. M. Oxidative alterations in Alzheimer's disease. Brain pathology (Zurich, Switzerland) 1999, 9(1), 133–146. doi.org/10.1111/j.1750-3639.1999.tb00215.x

49.- Herbert, V. Prooxidant effects of antioxidant vitamins. Introduction. The Journal of nutrition 1996, 126(4 Suppl), 1197S–200S.

50.- Hanna, P. A.; Ratkos, L.; Ondo, W. G.; & Jankovic, J. Switching from pergolide to pramipexole in patients with Parkinson's disease. Journal of neural transmission (Vienna, Austria : 1996) 2001, 108(1), 63–70. doi.org/10.1007/s007020170097

51.- Aguirre-Rueda, D.; Guerra-Ojeda, S.; Aldasoro, M.; Iradi, A.; Obrador, E.; Ortega, A.; et al. Astrocytes protect neurons from Aβ1-42 peptide-induced neurotoxicity increasing TFAM and PGC-1 and decreasing PPAR-γ and SIRT-1. International journal of medical sciences 2015a, 12(1), 48–56. doi.org/10.7150/ijms.10035

52.- Desagher, S.; Glowinski, J.; Premont, J. Astrocytes protect neurons from hydrogen peroxide toxicity. The Journal of neuroscience : the official journal of the Society for Neuroscience 1996, 16(8), 2553–2562. doi.org/10.1523/JNEUROSCI.16-08-02553.1996

53.- Allaman, I.; Gavillet, M.; Bélanger, M.; Laroche, T.; Viertl, D.; Lashuel, H. A.; Magistretti, P. J. Amyloid-beta aggregates cause alterations of astrocytic metabolic phenotype: impact on neuronal viability. The Journal of neuroscience: the official journal of the Society for Neuroscience 2010, 30(9), 3326–3338. doi.org/10.1523/JNEUROSCI.5098-09.2010

54.- Valles, S. L.; Dolz-Gaiton, P.; Gambini, J.; Borras, C.; Lloret, A.; Pallardo, F. V.; Viña, J. Estradiol or genistein prevent Alzheimer's disease-associated inflammation correlating with an increase PPAR gamma expression in cultured

astrocytes. Brain research 2010, 1312, 138–144. doi.org/10.1016/j.brainres.2009.11.044

55.- Aguirre-Rueda, D.; Guerra-Ojeda, S.; Aldasoro, M.; Iradi, A.; Obrador, E.; Mauricio, M. D.; Vila, J. M.; Marchio, P.; Valles, S. L. WIN 55,212-2, agonist of cannabinoid receptors, prevents amyloid β1-42 effects on astrocytes in primary culture. PloS one 2015, 10(4), e0122843. doi.org/10.1371/journal.pone.0122843

56.- Aldasoro, M.; Guerra-Ojeda, S.; Aguirre-Rueda, D.; Mauricio, M. D.; Vila, J. M.; Marchio, P.; Iradi, A.; Aldasoro, C.; Jorda, A.; Obrador, E.; et al. Effects of Ranolazine on Astrocytes and Neurons in Primary Culture. PloS one 2016, 11(3), e0150619. doi.org/10.1371/journal.pone.0150619

57.- Wang, X.; Michaelis, E.K. Selective Neuronal Vulnerability to Oxidative Stress in the Brain. Front Aging Neurosci 2010, 2. doi:10.3389/fnagi.2010.00012.)

58.- Hsu, L.J.; Sagara, Y.; Arroyo, A.; Rockenstein, E.; Sisk, A.; Mallory, M.; Wong, J.; Takenouchi, T.; Hashimoto, M.; Masliah, E. α-Synuclein Promotes Mitochondrial Deficit and Oxidative Stress. The American Journal of Pathology 2000, 157, 401–410. doi:10.1016/S0002-9440(10)64553-1.

59.- Scudamore, O.; Ciossek, T. Increased Oxidative Stress Exacerbates α-Synuclein Aggregation In Vivo. Journal of Neuropathology & Experimental Neurology 2018, 77, 443–453. doi:10.1093/jnen/nly024.

60.- Butterfield, D.A.; Boyd-Kimball, D. The critical role of methionine 35 in Alzheimer's amyloid β-peptide (1–42)-induced oxidative stress and neurotoxicity. Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics 2005, 1703, 149–156, doi:10.1016/j.bbapap.2004.10.014.

61.- Gandhi, S.; Abramov, A.Y. Mechanism of Oxidative Stress in Neurodegeneration. Oxidative Medicine and Cellular Longevity 2012, 2012, 1–11, doi:10.1155/2012/428010)

62.- Tönnies, E.; Trushina, E. Oxidative Stress, Synaptic Dysfunction, and Alzheimer's Disease. Journal of Alzheimer's Disease 2017, 57, 1105–1121, doi:10.3233/JAD-161088

63.- Tapias, V.; Hu, X.; Luk, K.C.; Sanders, L.H.; Lee, V.M.;Greenamyre, J.T. Synthetic alpha-synuclein fibrils cause mitochondrial impairment and selective dopamine neurodegeneration in part via iNOS-mediated nitric oxide production. Cellular and Molecular Life Sciences 2017, 74, 2851–2874, doi:10.1007/s00018-017-2541-x.

64.- Gao, J.; Wang, L.; Liu, J.; Xie, F.; Su, B.; Wang, X. Abnormalities of Mitochondrial Dynamics in Neurodegenerative Diseases. Antioxidants 2017, 6, 25, doi:10.3390/antiox6020025.

65.- Scudamore, O.; Ciossek, T. Increased Oxidative Stress Exacerbates α-Synuclein Aggregation In Vivo. Journal of Neuropathology & Experimental Neurology 2018, 77, 443–453, doi:10.1093/jnen/nly024

66.- Cudkowicz, M.E.; McKenna-Yasek, D.; Sapp, P.E.; Chin, W.; Geller, B.; Hayden, D.L.; Schoenfeld, D.A.; Hosler, B.A.; Horvitz, H.R.; Brown, R.H. Epidemiology of mutations in superoxide dismutase in amyotrophic lateal sclerosis. Annals of Neurology 1997, 41, 210–221, doi:10.1002/ana.410410212

67.- Beckman, J.S.; Carson, M.; Smith, C.D.; Koppenol, W.H. ALS, SOD and peroxynitrite. Nature 1993, 364, 584–584, doi:10.1038/364584a0

68.- Forsberg, K.; Jonsson, P.A.; Andersen, P.M.; Bergemalm, D.; Graffmo, K.S.; Hultdin, M.; Jacobsson, J.; Rosquist, R.; Marklund, S.L.; Brännström, T. Novel Antibodies Reveal Inclusions Containing Non-Native SOD1 in Sporadic ALS Patients. PLoS ONE 2010, 5, e11552, doi:10.1371/journal.pone.0011552

69.- Goswami, A.; Dikshit, P.; Mishra, A.; Mulherkar, S.; Nukina, N.; Jana, N.R. Oxidative stress promotes mutant huntingtin aggregation and mutant huntingtin-dependent cell death by mimicking proteasomal malfunction. Biochemical and Biophysical Research Communications 2006, 342, 184–190, doi:10.1016/j.bbrc.2006.01.136.

70.- Halassa, M. M.; Florian, C.; Fellin, T.; Munoz, J. R.; Lee, S. Y.; Abel, T.; Haydon, P. G.; Frank, M. G. Astrocytic modulation of sleep homeostasis and cognitive consequences of sleep loss. Neuron 2009, 61(2), 213–219. doi.org/10.1016/j.neuron.2008.11.024

71.- Brown, R. E.; Basheer, R.; McKenna, J. T.; Strecker, R. E.; McCarley, R. W. Control of sleep and wakefulness. Physiological reviews 2012, 92(3), 1087–1187. doi.org/10.1152/physrev.00032.2011

72.- Kang, J. E.; Lim, M. M.; Bateman, R. J.; Lee, J. J.; Smyth, L. P.; Cirrito, J. R.; Fujiki, N.; Nishino, S.; Holtzman, D. M. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. Science (New York, N.Y.) 2009, 326(5955), 1005–1007. doi.org/10.1126/science.1180962

73.- Haydon, P. G. Astrocytes and the modulation of sleep. Current opinion in neurobiology 2017, 44, 28–33. doi.org/10.1016/j.conb.2017.02.008

74.- Mawuenyega, K. G.; Sigurdson, W.; Ovod, V.; Munsell, L.; Kasten, T.; Morris, J. C.; Yarasheski, K. E.; Bateman, R. J. Decreased clearance of CNS beta-

amyloid in Alzheimer's disease. Science (New York, N.Y.) 2010, 330(6012), 1774. doi.org/10.1126/science.1197623

75.- Mawuenyega, K.G.; Sigurdson, W.; Ovod. V. et al. Decreased clearance of CNS beta-amyloid in Alzheimer's disease. Science. 2010, 330(6012), 1774. doi:10.1126/science.1197623

76.- Morris, G.; Stubbs, B.; Köhler, C. A.; Walder, K.; Slyepchenko, A.; Berk, M.; Carvalho, A. F. The putative role of oxidative stress and inflammation in the pathophysiology of sleep dysfunction across neuropsychiatric disorders: Focus on chronic fatigue syndrome, bipolar disorder and multiple sclerosis. Sleep medicine reviews 2018, 41, 255–265. doi.org/10.1016/j.smrv.2018.03.007

77.- Bortolon, C.; Macgregor, A.; Capdevielle, D.; Raffard, S. Apathy in schizophrenia: A review of neuropsychological and neuroanatomical studies. Neuropsychologia 2018, 118(Pt B), 22–33. doi.org/10.1016/j.neuropsychologia.2017.09.033

78.- Caeiro, L.; Ferro, J. M.; Costa, J. Apathy secondary to stroke: a systematic review and meta-analysis. Cerebrovascular diseases (Basel, Switzerland) 2013, 35(1), 23–39. doi.org/10.1159/000346076

79.- Ghavami, S.; et al. Autophagy and apoptosis dysfunction in neurodegenerative disorders. Prog Neurobiol. 2014, 112, 24–49

80.- Kiechle, T. et al. Cytochrome C and caspase-9 expression in Huntington's disease. Neuromolecular Med. 2002, 1(3), 183–195

81.- Li, S.H.; Lam, S.; Cheng, A.L.; Li, X.J. Intranuclear huntingtin increases the expression of caspase-1 and induces apoptosis. Hum Mol Genet. 2000, 9(19), 2859–2867

82.- Pasinelli, P.; Houseweart, M.K.; Brown, R.H.; Cleveland, D.W. Caspase-1 and -3 are sequentially activated in motor neuron death in Cu, Zn superoxide dismutase-mediated familial amyotrophic lateral sclerosis. Proc Natl Acad Sci U S A. 2000, 97(25), 13901–13906

83.- Garden, G.A.; et al. Caspase cascades in human immunodeficiency virus-associated neurodegeneration. J Neurosci. 2002, 22(10), 4015–4024

84.- Re, D.B. et al. Necroptosis drives motor neuron death in models of both sporadic and familial ALS. Neuron. 2014, 81(5), 1001–1008

85.- Ito, Y. et al. RIPK1 mediates axonal degeneration by promoting inflammation and necroptosis in ALS. Science. 2016, 353(6299), 603–608

86.- Ofengeim, D. et al. Activation of necroptosis in multiple sclerosis. Cell Rep 2015, 10(11), 1836–1849

87.- Levenson, R. W.; Sturm, V. E.; Haase, C. M. Emotional and behavioral symptoms in neurodegenerative disease: a model for studying the neural bases of psychopathology. Annual review of clinical psychology 2014, 10, 581–606. doi.org/10.1146/annurev-clinpsy-032813-153653

88.- Pagonabarraga, J.; Kulisevsky, J.; Strafella, A. P.; Krack, P. Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment. The Lancet. Neurology 2015, 14(5), 518–531. doi.org/10.1016/S1474-4422(15)00019-8

89.- Carnes-Vendrell, A. Deus, J.; Molina-Seguin, J.; Pifarré, J.; Purroy, F. Depression and Apathy after Transient Ischemic Attack or Minor Stroke: Prevalence, Evolution and Predictors. Sci Rep. 2019, 9(1), 16248. doi:10.1038/s41598-019-52721-5

90.- Cortes, N.; Andrade, V.; & Maccioni, R. B. Behavioral and Neuropsychiatric Disorders in Alzheimer's disease. Journal of Alzheimer's disease. JAD 2018, 63(3), 899–910. doi.org/10.3233/JAD-180005

91.- Christoforidou, E.; Joilin, G.; Hafezparast, M. Potential of activated microglia as a source of dysregulated extracellular microRNAs contributing to neurodegeneration in amyotrophic lateral sclerosis. Journal of neuroinflammation 2020, 17(1), 135. doi.org/10.1186/s12974-020-01822-4

92.- Takahashi, M.; Tabu, H.; Ozaki, A.; Hamano, T.; Takeshima, T. Antidepressants for Depression, Apathy, and Gait Instability in Parkinson's disease: A Multicenter Randomized Study. Intern Med. 2019, 58(3), 361-368. doi:10.2169/internalmedicine.1359-18

93.- Morris, G.; Berk, M.; Galecki, P.; Walder, K.; Maes, M. The Neuro-Immune Pathophysiology of Central and Peripheral Fatigue in Systemic Immune-Inflammatory and Neuro-Immune Diseases. Mol Neurobiol. 2016, 53(2), 1195-1219. doi:10.1007/s12035-015-9090-9

94.- Trapp, B.D.; Nave, K.A. Multiple sclerosis: An immune or neurodegenerative disorder? Annu. Rev. Neurosci. 2008, 31, 247–269.

95.- Baecher-Allan, C.; Kaskow, B.J.; Weiner, H.L. Multiple sclerosis: Mechanisms and immunotherapy. Neuron 2018, 97, 742–768.

96.- Thompson, A.J.; Baranzini, S.E.; Geurts, J.; Hemmer, B.; Ciccarelli, O. Multiple sclerosis. Lancet 2018, 391, 1622–1636. 8

97.- Liu, S.; Park, S.; Allington, G.; Prelli, F.; Sun, Y.; Martá-Ariza, M.; Scholtzova, H.; Biswas, G.; Brown, B.; Verghese, P. B.; et al. Targeting Apolipoprotein E/Amyloid β Binding by Peptoid CPO_Aβ17-21 P Ameliorates Alzheimer's Disease Related Pathology and Cognitive Decline. Scientific reports 2017, 7(1), 8009. doi.org/10.1038/s41598-017-08604-8

98.- Chang, W. S.; Wang, Y. H.; Zhu, X. T.; Wu, C. J. Genome-Wide Profiling of miRNA and mRNA Expression in Alzheimer's Disease. Medical science monitor. International medical journal of experimental and clinical research 2017, 23, 2721–2731. doi.org/10.12659/msm.905064

99.- Beckman, J.S.; Carson, M.; Smith, C.D.; Koppenol, W.H. ALS, SOD and peroxynitrite. Nature 1993, 364, 584–584. doi:10.1038/364584a0

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Figures

Figure 1: Neurons in primary culture (7 days). Neurons and Radial glia are detected. Phase contrast microscope.

Figure 2: Disorders with microglia or immune involvement. Different illness and their relationship

Figure 3: Astrocytes in primary culture Aβ1-42 (A) or Aβ1-42 (B). 6 h with 5 μM Aβ40-1 (control) or Aβ1-42 (Aβ). Aβ1-42 increases mitochondrial aggregation in astrocytes in primary culture. Confocal microscopy: Mitotracker (250 nM) to stain mitochondria and Hoechst 33342 (2 μg/ml) to stain nuclei.

Figure 4: Communication between astrocytes, neurons and microglia in pain situations. Activation of nociceptors cause the induction of cytokines, chemokines, BDNF and neurotrophic factors producing changes an increase of persistent pain.

Figure 5: Live cells attached to plaque. Number of astrocytes in primary culture with or without Aβ1-42. D4,5,6,7 (day of culture). Aβ was added the 4th day of culture.

Figure 6: Healthy physiologically astrocytes. Release of neurotrophic factors and antioxidants, ion homeostasis, detoxification of ROS/RNS, fluid transport, vasodilation and neurotransmitter reuptake.

Figure 7: Reactive astrocytes. Release cytokines and chemokines, ROS/RNS production, increased expression of GFAP, vimentin and Glu, compensatory release of antioxidants