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Role of Astrocytes in the pathogenesis of Alzheimer's Disease: A Narrative Review.

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Abstract

Alzheimer's disease (AD) is a type of dementia that leads to cognitive and functional decline that worsens throughout disease progression. Although there is not a final theory when it comes to the disease's pathogenesis, it is known that the disease mechanism involves the deposition of β-amyloid plaques and hyperphosphorylation of tau proteins in the brain, which leads to neurodegeneration and neuronal death. Astrocytes are a type of glial cell that are known to play numerous complex and essential roles in various aspects of neuronal function, mainly through the release of gliotransmitters like glutamate and D-serine. Through the release gliotransmitters, astrocytes can modulate cerebral processes, synaptic transmission and neuronal excitability and, through this, help to maintain a healthy and functioning central nervous system. There is evidence that points to astrocytes having an active role in the pathogenic process of AD, seeing as they express genes that are associated to a higher risk of developing AD; they also undergo morphological, molecular and functional changes in the AD affected brain, leading to the appearance of phenotypes that have been shown to promote neurotoxicity and cell death, through the dysregulation of gliotransmitter release and reuptake, especially glutamate and D-serine. Due to this, and especially since the current therapeutic options available for the treatment of AD are limited and mostly purely symptomatic, with no effective curative options, I wrote this work to review what is currently known about astrocytes and their role in AD pathogenesis in the currently published scientific literature, and in doing so, evaluate the worth of future investigations in this field by compiling all the relevant information I found in an easy to access, narrative text review.

Keywords: Alzheimer's disease; astrocytes, neurodegeneration, glutamate, D-serine

Resumo

A Doença de Alzheimer (AD) é um tipo de demência que leva a declínio cognitivo e funcional, agravado com a progressão da doença. Embora não haja uma teoria definitiva no que diz respeito à patogénese desta doença, sabe-se que o seu mecanismo passa pela deposição de placas de β-amiloide e de proteinas tau hiperfosforiladas ao nível do cérebro, culminando em neurodegeneração e morte neuronal. Os astrócitos são um tipo de células gliais que desempenham numerosos papéis complexos e essenciais em várias vertentes do funcionamento neuronal, maioritariamente através da libertação de gliotransmissores como o glutamato e a D-serina. Através da libertação destes gliotransmissores, os astrócitos modulam processos como a transmissão sináptica e a excitabilidade neuronal, ajudando assim a manter o sistema nervoso central saudável e funcional. Várias evidências mostram que os astrócitos têm um papel ativo na patogénese da AD, pois expressam genes que estão associados a um maior risco de desenvolvimento da doença. Os astrócitos sofrem também alterações morfológicas, moleculares e funcionais na AD, levando ao aparecimento de fenótipos celulares que promovem neurotoxicidade e morte celular, maioritariamente através da disregulação da libertação e reuptake de gliotransmissores como o glutamato e a D-serina. Assim, e especialmente pelo facto das opções terapêuticas actuais para o tratamento de AD serem maioritariamente sintomaticas, sem existir terapêutica curativa eficaz, escrevi este trabalho para rever a informação existente na literatura cientifica acerca do papel dos astrócitos na patogénese da AD e assim avaliar o eventual valor de futuras investigações nesta área através da compilação de toda a informação relevante que encontrei numa revisão narrativa de fácil acesso.

Palavras-chave: Doença de Alzheimer, astrócitos, neurodegeneração, glutamato, D-serina

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List of Abbreviations

Aβ	Amyloid Beta
Ach	Acetylcholine
AD	Alzheimer's Disease
ALS	Amyotrophic Lateral Sclerosis
AMPAR	AMPA receptor
ANLS	Astrocyte-neuron lactate shuttle
ApoE / ApoJ	Apolipoprotein E / Apolipoprotein J
APP	Amyloid precursor protein
Asc-1	Alanine/serine/cysteine transporter 1
ASCT	Alanine/serine/cysteine/threonine transporter
ATP	Adenosine Triphosphate
BDNF	Brain-derived neurotrophic factor
BLA-ACC	Basolateral amygadala-anterior cingulate cortex
CNS	Central Nervous System
CTE	Chronic Traumatic Encephalopathy
DAB	Glycogen phosphorylase inhibitor 1,4-didioxy-1,4-imino-D-arabinitol
DLP	Depressive-like phenotype
FTLD-TDP	Frontotemporal lobar degeneration associated with TDP-43 pathology
GABA	γ-Aminobutyric acid
GAT-3	GABA transporter 3
EAAT1/2/GLAST	Excitatory amino acid transporter 1/2 / Glutamate Aspartate Transporter
GLT-1	Glutamate transporter 1
GLP1R	Glucagon Like Peptide 1 Receptor
GPCR	G-protein coupled receptor
IP3	Inositol triphosphate
IP3R2	Inositol triphosphate receptor 2
LTD / LTP	Long-term depression / long-term potentiation
PD	Parkinson's Disease
PFC	Pre-frontal cortex
PHGDH	Phosphoglycerate Dehydrogenase
PrPC	Cellular prion protein
PrPSc	Scrapie isoform of the prion protein
PSEN1 / PSEN2	Presenilin-1/2
ROS	Reactive oxygen species
mGluR	Metabotropic glutamate receptor
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
NAc	Nucleus Accumbens
NMDAR	N-methyl-D-aspartate receptor /
SSRI	Selective serotonin receptor inhibitors
TDP-43	TAR DNA-binding protein 43
TNF-α	Tumor Necrosis Factor-alpha
TRPC1	Transient Receptor Potential Cation Channel 1
VGLUT	Vesicular Glutamate Transporter
VRAC	Volume-regulated anion channel

1| Neuroglia, astrocytes, and brain function

Rudolf Virchow introduced the concept of neuroglia in 1856, characterizing it as a group of cells that belonged to the Nervous System that were incapable of generating electrical impulses and that, due to this, were primarily support elements for the functional maintenance of neurons, acting as a sort of "neuron glue" (Virchow, 1860; Kettenmann & Verkhratsky 2008). Throughout the 19th century, various authors proposed numerous hypotheses over the function that these types of cells could have: Camillo Golgi proposed in 1870 that glial cells could be responsible for the metabolic communication between blood vessels and neurons (Verkhratsky & Butt 2013); Santiago Ramón y Cajal later went on to defend that glial cells could have a role in controlling the diameter of the blood vessels in the brain (Verkhratsky & Butt 2013); Carl Ludwig Schleich on another hand proposed in 1989 that these cells could be involved in inhibitory mechanisms that controlled neuronal communication (Kettenmann & Verkhratsky 2008).

In 1893, Michael von Lenhossek presented the idea that various types of cells belonged to Neuroglia, using the characteristic star-shaped morphology of astrocytes to differentiate them from microglia and oligodendrocytes (Matyash & Kettenmann 2010). At the current time, four main families of cells are considered as a part of the neuroglia family of cells: microglia, oligodendrocytes, NG2+ cells, and astrocytes (Maldonado et al. 2011), with each of them performing very important and fundamental roles in the functioning and maintenance of the nervous system (Sofroniew & Vinters 2010). Oligodendrocytes are involved in the myelination of neuronal dendrites and the repair of the damaged myelin sheet of neurons, while also being known to secrete neurotrophic factors like brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) to provide neuronal support (Bradl & Lassmann 2010). Meanwhile, microglia have an important active immunological role in the Central Nervous System (CNS), especially when there is infection and/or inflammation of the brain tissue (Wake et al. 2011). On another hand, NG2+ cells have been shown to be capable of forming synapses with neurons (Bergles et al. 2000; De Biase et al. 2010),

while also being known to be precursor cells to oligodendrocytes, being able to differentiate into this type of cell when faced with various stimuli, like myelin damage (Gensert & Goldman 1997; Zawadzka et al. 2010).

Astrocytes are known to play numerous complex and essential roles in various aspects of neuronal function, being involved in synaptic transmission and neuronal excitability while also helping to maintain a healthy and functioning CNS (Sofroniew & Vinters 2010; Perea & Araque 2010; Khakh & Sofroniew 2015). These cells play a role in the physiology and development of the CNS, helping with trophic support through their uptake of glucose and subsequent glycolysis of this substance, which ends up releasing lactate as a metabolic substrate to be used by neurons (Cajal 1911; Tsacopoulos & Magistretti 1996). Astrocytes are also capable of secreting neurotrophic factors, playing a role in neuronal survival and differentiation (Raff et al. 1993; Takeshima et al. 1994). They also play a role in neuronal guidance during the developmental stages of the brain, through their formation of direct neuron-glial cell interactions (Kuwada 1986; Rakic 1990). On another hand, astrocytes are also involved in controlling synaptic efficacy, potentiating synaptogenesis and synaptic activity and plasticity (Mauch et al. 2001; Pfrieger & Barres 1997; Perea & Araque 2007) and in neurite outgrowth through their secretion of soluble astrocyte-derived substances (Le Roux & Reh 1994; Smith et al. 1990). Finally, astrocytes also contribute to brain homeostasis through their selective secretion and reuptake of neuroactive substances like neurotransmitters and neuromodulators through the activity of specific transporters (Largo et al. 1996; Bergles & Jahr 1997; Mennerick & Zorumski 1994), and also through the regulation of local ion concentrations through several types of ion pumps and channels that are present in their membranes (Largo et al. 1996; Orkand et al. 1966; Perea & Araque 2002).

1.1| The Tripartite Synapse

The tripartite synapse is a neurophysiological concept of bidirectional communication between neurons and astrocytes, in which astrocytes exchange

information with the pre-synaptic and post-synaptic neurons (the synaptic neuronal elements) in response to synaptic activity, which leads to the regulation and/or modulation of synaptic function (Perea et al. 2009). This however does not happen through the generation of electrical stimulus, as astrocytes are incapable of generating action potentials (Orkand et al. 1966; Sontheimer 1994; Verkhratsky & Steinhäuser 2000; Seifert & Steinhäuser 2001). While incapable of generating action potentials, astrocytes do possess excitability through variations of their intracellular calcium concentrations. This was shown in fluorescent imaging studies conducted in the 1990s where it was observed that a rise in intracellular calcium concentration inside of the astrocytes (through the mobilization of the stores of this ion inside the endoplasmic reticulum) served as an intracellular signal and as the main agent through which most astrocytes' cellular responses were triggered. Other studies have further shown that elevations of intracellular astrocytic calcium concentrations can occur on one hand in response to the release of neurotransmitters from the pre-synaptic terminal during synaptic activity (Perea & Araque 2005) but also on another hand as spontaneous intrinsic oscillations even when no neuronal activity is present (Aguado et al. 2003; Nett et al. 2002; Parri et al. 2001). This in itself is of high importance, because it demonstrates that neuron-to-astrocyte communication does indeed exist.

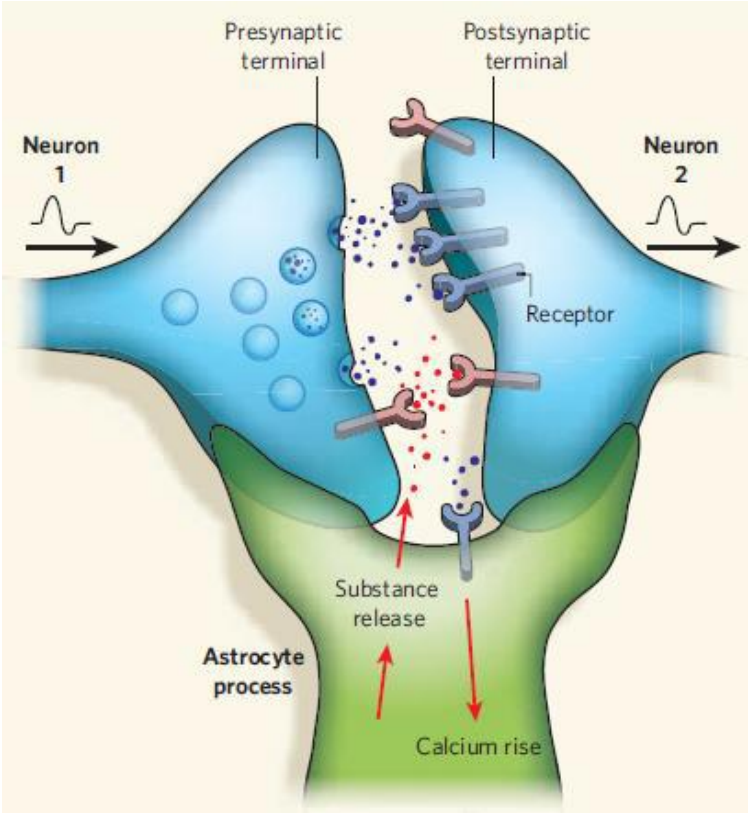

Figure 1: The tripartite synapse model (Adapted from Allen and Barres, 2009).

1.1.1| Ca^{2+}-dependent gliotransmission

In the membrane of astrocytes exists a wide variety of receptors for neurotransmitters, that include glutamate, GABA, adenosine, norepinephrine, histamine, and acetylcholine (Ach), so when the presynaptic terminal releases a neurotransmitter into the synaptic cleft, these neurotransmitters will bind to either their post-synaptic or astrocytic membrane receptors, which in turn ends up causing cellular responses (Porter & McCarthy 1997; Halassa et al. 2007). The neurotransmitter receptors present in the astrocytic cell membranes are mostly G-protein coupled receptors (GPCRs), which means that their activation triggers the phospholipase C pathway, leading to the formation of inositol (1,4,5)-triphosphate (IP3) and consequently its binding to the IP3R2 receptor at the endoplasmic reticulum, which triggers the mobilization of the calcium stores that exist inside this organelle into the

cytosol (Lev-Ram and Ellisman, 1995; Poskanzer and Yuste, 2011; Santello et al. 2012, 2016). Normally, while in physiological conditions, there is a tight control of the intracellular calcium concentrations of each cell, due to the fact that any shifts in the homeostasis of this ion can lead to cellular dysfunction and culminate in cell death (Ronco et al. 2014). In the case of astrocytes, however, these brief increases of intracellular Ca^{2+} enables these cells to respond to neuronal activity, through the release of specific chemical, neuroactive substances called gliotransmitters (Araque et al., 2014; Halassa et al., 2007; Perea and Araque, 2010; Perea et al., 2009; Santello et al., 2012; Savtchouk and Volterra, 2018; Kofuji and Araque, 2021a). It's also been shown that these glial Ca^{2+} signals are not restricted to the cell they are generated at, being able to propagate through the astrocytic network of cells as a calcium wave (Cornell-Bell et al., 1990; Schipke et al., 2002), which leads to an amplification of the neuronal signals (Chen et al. 2019).

It is also interesting to note that recent studies have shown that astrocytic processes possess a high level of Ca^{2+} activity that are often uncorrelated with increases in intracellular calcium that happen in the astrocytic cell body (Shigetomi et al., 2013; Otsu et al., 2015; Poskanzer and Yuste, 2016; Ye et al., 2017; Bindocci et al., 2017; Stobart et al., 2018; Kofuji and Araque, 2021a), which suggests that they might be the subject of local modulation (Volterra et al., 2014; Kofuji and Araque, 2021a). This might mean that the calcium sources that trigger these spontaneous signals in astrocytic processes microdomains originate from alternate sources than from IP3R2 signalling, such as mitochondrial release or the opening of TRPC1 channels (Malarkey et al., 2008a; Agarwal et al., 2017; Kofuji and Araque 2021a), seeing as they remain mostly unaffected when using IP3R2 knockout mouse models (Stobart et al., 2018). However, the general agreement in the scientific community is that despite this, GPCR activation seems to lead to a higher probability of Ca^{2+} signalling happening in the microdomains of astrocytes, and that at higher levels of activation these signals end up being transmitted to the astrocytic cell body (Araque et al., 2014; Volterra et al., 2014; Kofuji and Araque, 2021a).

Astrocytes perform most of their functions through the release of chemical, neuroactive messengers, called gliotransmitters. The mechanisms through which gliotransmission occurs is still a subject that is actively studied (Kofuji and Araque 2021a), but there are many studies that seem to indicate that the release of gliotransmitters by astrocytes is mainly done through the calcium and SNARE-complex dependent processes (Araque et al., 2000; Bezzi et al., 2004; Bohmbach et al., 2018; Perea and Araque, 2005; Schwarz et al., 2017; Savtchouk and Volterra, 2018; Kofuji and Araque 2021a) which enables astrocytes cells to respond to neuronal activity through the release of specific gliotransmitters, depending on the situation.

However it is also important to note that astrocytes can also release gliotransmitters through diffusion via non-exocitotic pathways like volume-regulated anion channels, Ca^{2+}-dependent anion channel bestrophin 1, two-pore potassium channels, hemichannels/connexins or pore-forming P2X7 receptors; or mediated by specific transporters (cysteine-glutamate exchanger, reversal of uptake by glutamate (GLT-1 and GLAST) and GABA transporters (GAT-3)) (Duan et al., 2003; Kimelberg et al., 2006; Zhou et al., 2009; Hamilton and Attwell, 2010; Park et al., 2013; Montero and Orellana, 2015). Astrocytic glutamate has also been shown to be able to be released through volume-regulated anion channels (VRAC) (Gundersen et al., 2015). So far several gliotransmitters have been identified, including glutamate (Angulo et al. 2004), adenosine triphosphate (ATP) (Coco et al. 2003), D-serine (Oliet & Mothet 2009), GABA (Yoon & Lee 2014), brain-derived neurotrophic factor (BDNF) (Bergami et al. 2008), prostaglandins (Clasadonte et al., 2011), thrombospondin (Eroglu et al., 2009), and even tumor necrosis factor alpha (TNF-α) (Beattie et al. 2002; Stellwagen and Malenka, 2006). In this thesis I will focus on glutamate and D-serine due to their importance for AD pathogenesis.

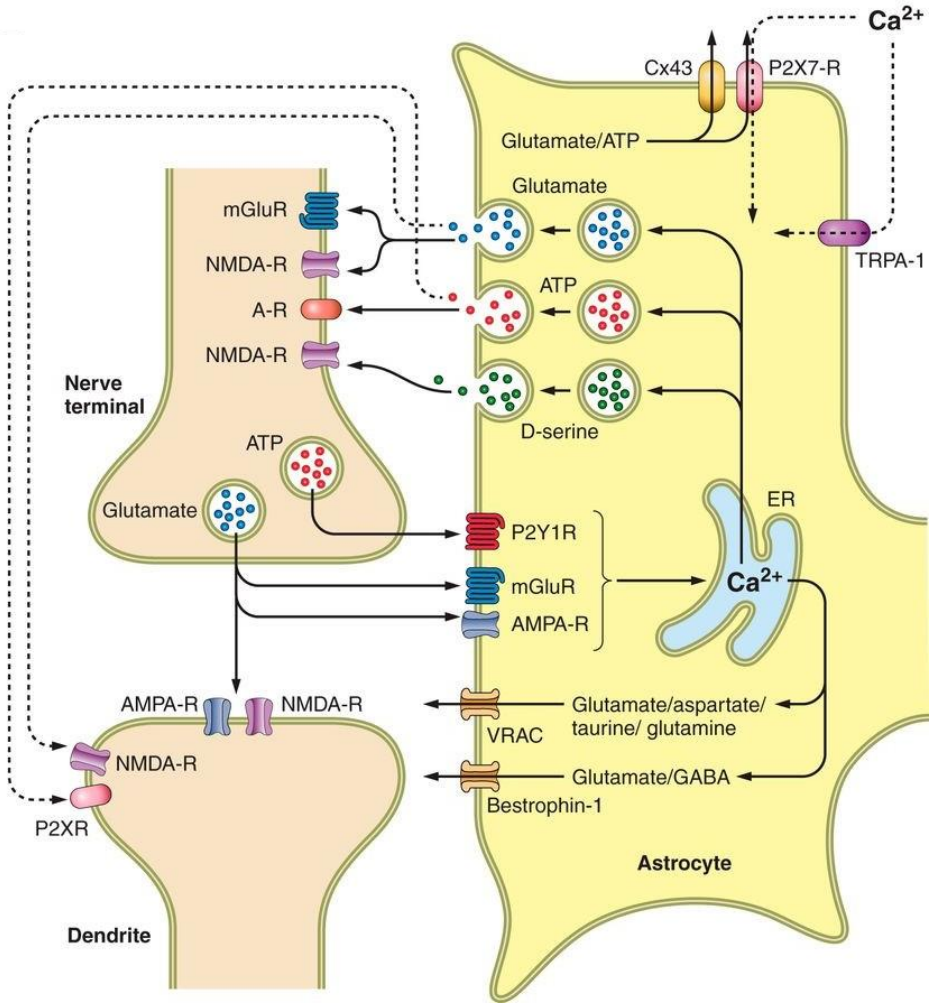

Figure 2: Model of Ca^{2+} dependent gliotransmission (Adapted from Gundersen et al. 2015)

1.1.2| Gliotransmitters: glutamate and D-serine

Gliotransmitters are a group of substances that are neuroactive and that are released by astrocytes into the synaptic cleft, which include glutamate (Angulo et al. 2004), ATP (Coco et al. 2003), D-serine (Oliet & Mothet 2009), and GABA (Yoon & Lee 2014), among others. The release of these gliotransmitters into the synaptic cleft, and the consequent interaction between these substances and their respective receptors (located in the pre-synaptic neuron and the post-synaptic neuron) is what leads to the

modulation and/or regulation of synaptic events, depending on the type of gliotransmitter that is released (Allen & Barres 2009).

Astrocytes play a role in both the uptake and the release of glutamate from and into the synaptic cleft, which leads to them being a very important factor in the establishment of the homeostasis of this substance, which supports brain function and protects against neuroexcitotoxicity triggered by high concentration of glutamate (Mahmoud et al., 2019). It has been described that glutamate is stored in astrocytic vesicles present in perisynaptic processes through the activation of vesicular glutamate transporters (VGLUTs) (Bergersen et al., 2012; Harada et al., 2015), being released through an Ca^{2+}-dependent exocytotic pathway spontaneously or in response to neuronal activity (Araque et al., 2000; Bezzi et al., 2004; Zhang et al., 2004; Malarkey and Parpura, 2008b). The clearance of glutamate is mainly done through the astrocyte-specific EAAT1 and EAAT2 glutamate transporters (Lanciotti et al., 2013). Glutamate is the main excitatory neurotransmitter in the brain that serves as a direct contributor to synaptic plasticity (Hu et al., 2016), and through its release astrocytes are capable of modulating synaptic transmission, through the activation of either presynaptic, synaptic or extrasynaptic glutamate receptors, which can be ionotropic, like AMPARs, kainate receptors and NMDARs (Angulo et al., 2004; López-Hidalgo and Schummers, 2014) or metabotropic mGluRs (Araque et al., 1998; Perea and Araque, 2007).

D-serine is a substance that acts as a co-agonist of NMDA receptors (Coyle et al., 2020; Martineau et al., 2014), having an active role in neurotransmission, long-term potentiation and its related processes (Oliet & Mothet 2009; Henneberger et al., 2010). Although there is much discussion about the main origin of D-serine in the brain, a recent hypothesis by Wolosker in 2011 called the Serine Shuttle hypothesis has been mostly accepted as an explanation to the nature of D-serine dynamics in the central nervous system: astrocytes serve as the main source of *de novo* L-serine, due to the fact that they express Phosphoglycerate Dehydrogenase (PHGDH), the enzyme responsible for converting glucose into L-serine ,which is used to produce new D-serine in neurons (Wolosker, 2011; Ivanov and Mothet, 2019; Martineau et al., 2014). L-serine that is produced by astrocytes is then transported to the neurons through the

alanine/serine/cysteine/threonine transporter (ASCT), and then by the neuronal alanine/serine/cysteine transporter 1 (Asc-1), where it is used by serine racemase (SR) to produce new D-serine (Wolosker, 2011). Afterwards, D-serine is released by neurons and stored by astrocytes (Wolosker, 2011). D-serine released by astrocytes into the synaptic cleft in response to neuronal activity then binds to NMDAR, promoting functional plasticity at synapses (Wolosker, 2011): It has also been shown that the induction of LTP in the synapses of Schaffer collateral CA1 pyramidal neurons is dependent on the presence of intact glial cells and extracellular D-serine in experiments using hippocampal slices (Yang et al., 2003); D-serine has been shown to impact LTP by enabling the induction of LTP through the enhancement of NMDAR activation (Yang et al., 2003). Astrocytic D-serine also seems to play a part in the synaptic mechanisms of learning and memory, with a deficit of NMDAR activation and impairments in the biosynthesis of D-serine having been shown to exist in memory and learning impairments that appear during physiological aging (Mothet et al., 2006)

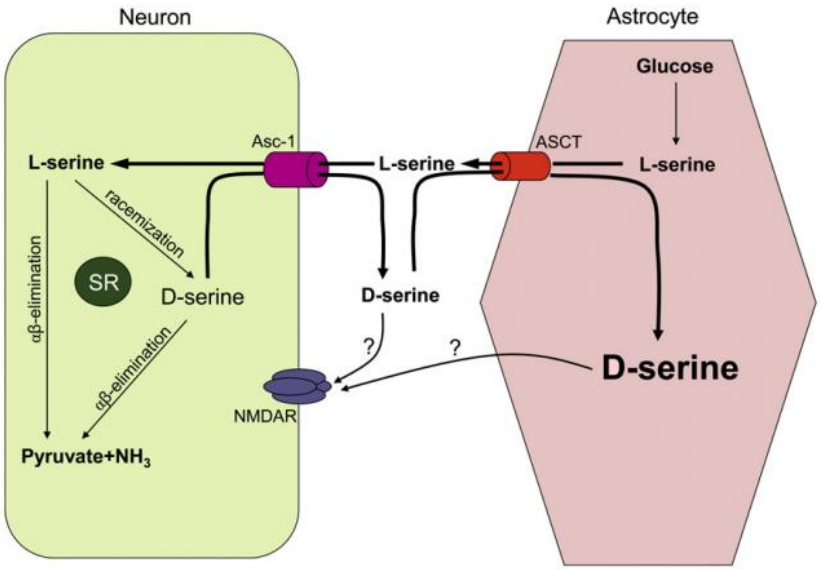

Figure 3: Model of the D-serine shuttle hypothesis (Adapted from Wolosker et al. 2011)

1.2.| Neuromodulation by Astrocytes

Astrocytes are linked together through gap junctions that connect them and allow them to work as a syncytium to propagate signals across the astrocytic cell network (Halassa et al., 2007). These gap junctions are comprised of connexon pairs that connect the cytoplasm of two adjacent cells (Nagy et al., 2001; Johnson et al., 2018; Hofer and Dermietzel, 1998; Wei et al., 2004; Wilson and Mongin, 2019) and they enable astrocytes to perform several functions like the facilitation of electrical and chemical communication between cells, alteration of the rhythm of neurons in the brainstem, changes in the distribution of K^+ ions across cells following a concentration gradient and also the transportation of small molecules like glucose across membranes according to cell needs (Kettenmann and Ranson, 1988; Kadala et al., 2015; Huguet et al., 2016; Condamine et al., 2018). Moreover, some brain functions that have been shown to be influenced by astrocytic neuromodulation include drug addiction, circadian rhythm, sleep-wake cycles, feeding behaviours and even sensory-motor responses (Kofuji and Araque, 2021b).

Noradrenaline and serotonin both have been shown to exert powerful effects on the metabolism of astrocytes: adrenergic agonists can alter the astrocytic metabolism by an increase of ATPase activity and also prime astrocytes for local changes in circuitry and alterations in behavioural state (Kimelberg et al., 1978; Cambray-Deakin et al., 1988; Paukert et al., 2014), while serotonin has been shown to alter K^+ permeability in glial cells (Hösli et al., 1993). It has been hypothesized that a disruption of the serotoninergic and adrenergic pathways may lead to a breakdown in the functional communication between neurons and glial cells, which could lead to neuronal degradation and as such contributing to the progression of Alzheimer's disease (Hertz, 1989). On another hand, Ach has been found to affect the trigger GABAergic transmission in astrocytes by causing increases in intracellular Ca^{2+} in these cells, leading to the release of glutamate (Banerjee et al., 2012; Beggiato et al., 2013; Wang et al., 2013), which ends up affecting the activity of astrocytic network oscillations. Besides that, it has been shown that the dopaminergic transmission blockade in the substantia nigra can cause morphological alterations that

resemble those found in Parkinson's disease, by provoking an increase in the calcium activity of astrocytes and through the formation of gap junctions between these cells (Bosson et al., 2015), which may be indicative that neuron-glia communication may play an active part in the pathophysiology of this disease. Finally, histamine has been suspected of playing a role in increasing the excitability of neurons and the astrocytic uptake of Ca^{2+}, which has been shown in *in vitro* experiments (Jung et al., 2000). Due to all this, further studies about these interactions between neurotransmitters and neuromodulators and their effects on astrocytic processes can possibly enrich our knowledge about the role that astrocytes play in healthy and pathological brains (Stevenson et al. 2020).

Memory and learning is another important field in which astrocytic neuromodulation seems to have a role in (Kofuji and Araque, 2021b). Although this was a controversial field for a very long time, recent studies have shown that Ca^{2+}-mediated gliotransmitter release by astrocytes has a direct influence over memory, with Pinto-Duarte and his team showing that IP3R2-knockout mice indeed had impaired long-term memory when compared to controls, performing much worse than these in all performed memory tests (Pinto-Duarte et al. 2019; Kofuji and Araque, 2021b). The Goshen group also showed interesting results through gain of function experiments, with chemogenetic activation of astrocytes in the CA1 hippocampus promoting an increase in neuronal activity and triggering LTP, with consequent better learning and performance in the memory tasks (Adamsky et al. 2018; Kofuji and Araque, 2021b). Other experiments using melanopsin to activate Gq pathway astrocytes also showed an induction of LTP in synapses, leading to improved memory performance (Mederos et al. 2019; Kofuji and Araque, 2021b).

The astrocyte-neuron lactate shuttle (ANLS) (Calì et al. 2019) is another example of astrocyte-neuronal signalling that seems to have an important role in late-term memory processes: Suzuki *et al* showed in 2011 that it could be observed that astrocytic glycogenolysis during learning acquisition wasn't needed for short-term memory but was otherwise integral for long-term memory, due to the fact that the chemically induced blockade of glycogenolysis using glycogen phosphorylase inhibitor 1,4-didioxy-

1,4-imino-D-arabinitol (DAB) prevented long-term memory retrieval but did not affect short-term memory (Suzuki et al., 2011; Kofuji and Araque, 2021b). This might probably be due to the fact that astrocytic glicogenolysis results in lactate release from astrocytes which is then used by neurons to fuel the memory consolidation process (Brown et al. 2004; Dringen et al. 1993; Steinman et al. 2016; Kofuji and Araque, 2021b).

LTD is another process that seems to be modulated by astrocytic activity as well (Kofuji and Araque, 2021b). Brigman et al have shown that in LTD-impaired mouse models which have intact LTP have deficits while performing hippocampal-dependent memory tasks (Brigman et al. 2010; Kofuji and Araque, 2021b). This was also shown through mouse models with a deletion of astrocytic p38a (a key signalling molecule involved in LTD), where this mutation prevented the triggering of LTD and even led to an increased freezing response in contextual fear-conditioning tasks and therefore a deficit in LTD-dependent long-term memory (Navarrete et al.2019; Kofuji and Araque, 2021b).

Astrocytic neuromodulation also seems to play an active role in emotional states (Kofuji and Araque, 2021b): Many studies have shown implications of astrocyte involvement underlying some forms of depressive-like phenotypes (DLP), with manifestations of anhedonia and behavioral despair after poisoning of the prefrontal cortex (PFC) astrocytes of adult rats (Banasr and Duman 2008; Kofuji and Araque, 2021b) and through the disruption of the gap-junction network of astrocytes and through the blocking of glutamate reuptake in the PFC. DLP-like behavior was also witnessed in experiments involving IP3R2-knockout mouse models and dnSNARE mice with impaired Ca^{2+} signalling or gliotransmission (Cao et al., 2013; Kofuji and Araque, 2021b), and on another hand, these same studies showed that ATP administration in the PFC reduced these same behaviours (Cao et al., 2013; Kofuji and Araque, 2021b). Other studies have also shown that insulin receptors seem to be linked to this phenomenon, with a lack of insulin receptor in astrocytes leading to a decrease in the release of ATP by astrocytes and culminating in decreased purinergic signalling in dopaminergic neurons (Cai et al., 2018; Kofuji and Araque, 2021b). This even seems to be one of the ways fluoxetine exerts its antidepressant effect, by causing an increase in the release of ATP by

astrocytes (Kinoshita et al. 2018). On another hand, astrocyte dysregulation also seems to play a role in drug addiction, especially through a decrease in expression and function of GLT-1 in the Nucleus Accumbens (NAc), leading to deficits in the homeostasis of glutamate, which can contribute to eventual relapse susceptibility through the activation of the PFC-NAc pathway (Das et al. 2015; Gipson et al. 2013; Knackstedt et al. 2010; Reissner et al. 2014, 2015; Shen et al. 2014; Scofield & Kalivas 2014; Kofuji and Araque, 2021b). Additionally, gliotransmission also seems to be involved as one of the underlying mechanisms that leads to fear-conditioned memory formation in the amygdala (Kofuji and Araque, 2021b).

Astrocytes also seem to have some power over the process of decision-making (Kofuji and Araque, 2021b). Some studies have shown that rats with chronic visceral pain and hypersensitivity have worse decision-making capabilities in the rodent gambling task when compared to controls, which was correlated to decreases in LTP and spike-field coherence in the basolateral amygadala-anterior cingulate cortex (BLA-ACC) network and that the dysfunction of lactate transfer from astrocytes to neurons also contributes to this (Cao et al., 2016; Wang et al., 2017; Kofuji and Araque, 2021b). It was also shown that exogenous infusion of lactate in the anterior cingulate cortex rescued these deficits and that optogenetic astrocyte activation produced the same results (Kofuji and Araque, 2021b). Due to this, it can be concluded that the astrocytic lactate shuttle is responsible for the optimization of the BLA-ACC network, which results in better decision-making performance (Kofuji and Araque, 2021b). Gliotransmission also seems to play a role in decision-making, which was shown through experimentation with zebrafish: Mu et al in 2019 managed to observe that there were Ca^{2+} responses in the astrocytic network of the brainstem when these animals were exposed to repeated bouts of swimming episodes with no perceptual movement, which is perceived as a futile action and leads to a passive behavioral state of giving up on swimming (Mu et al., 2019; Kofuji and Araque, 2021b). This is triggered by the astrocytes receiving inputs from noradrenergic neurons that detect failures in swimming which, when a threshold is reached, lead to an activation of the GABAergic neuron network by astrocytes that leads to the zebrafish giving up on swimming (Mu et al., 2019; Kofuji and Araque, 2021b).

Another example of this is the fact that some interneuron types in the hippocampus are capable of generating long-lasting trains of action potentials following repeated depolarizations, whose signals are detected by astrocytes and, when a threshold is reached, leads to the activation of inhibitory interneurons (Deemyad et al., 2018; Kofuji and Araque, 2021b). As such, we can conclude that astrocytes function as signal integrators to perform computations that are critical for decision-making in these kinds of neuronal networks (Kofuji and Araque, 2021b).

2| Neurodegenerative diseases

Neurodegeneration is the process involved in the progressive loss of structure and function of neurons, leading to their death (Bredesen et al. 2006). Many diseases, called neurodegenerative diseases, occur as a result of this process, which makes it so that they are normally considered incurable. Neurodegeneration can be found at all levels of the neuronal circuitry, from molecular to systemic (Bredesen et al. 2006). These neurodegenerative disorders can be classified based on their clinical presentation, being classified into pyramidal and extrapyramidal movement disorders or behavioural or cognitive disorders (Dugger & Dickson, 2017). It is also important to note that most patients have mixed clinical features, rarely there being “pure” syndromes (Dugger & Dickson, 2017).

Neurodegenerative diseases can be caused by a wide variety of mechanisms, which include genetic mutations, protein misfolding, alterations of protein degradation pathways, membrane damage, mitochondrial dysfunction, DNA damage, changes in axonal transport, induction of programmed cell death (apoptosis) and changes in function of the transglutaminase enzyme (Bredesen et al. 2006).

Some neurodegenerative diseases are the result of genetic mutations, some of which are found in completely unrelated genes. Many of these diseases share a common feature in the sense that they possess CAG nucleotide triplet repeats with different

degrees of severity, forming what is called a polyglutamine tract (polyQ). These disorders are as such named trinucleotide repeat disorders (Marsh et al. 2009; Thompson et al. 2008). Polyglutamine repeats normally cause dominant pathogenesis, which includes Huntington's disease and spinocerebellar ataxias (Zoghbi & Orr, 2009).

Most neurodegenerative diseases are a consequence of the aggregation of misfolded proteins, being as such classified as proteopathies (Dugger & Dickson, 2017). Different protein aggregates are involved in these types of neurodegenerative diseases, like alpha-synuclein, tau, beta-amyloid, TDP-43 and prions. Alpha-synuclein is capable of aggregation in order to form insoluble fibrils, called Lewy bodies, that are involved in diseases like Parkinson's disease, dementia with Lewy bodies and multiple system atrophy (Spillantini et al. 1997; Lantos, 1998; Dugger & Dickson, 2017). It has also been shown that fragments of alpha-synuclein (non-Abeta component or NAC) are present in amyloid plaques in Alzheimer's disease (Ueda et al. 1993). Meanwhile, hyperphosphorylated tau protein is the primary structural component that forms neurofibrillary tangles (NFTs) that are present in Alzheimer's disease, while beta-amyloid is the major component of senile plaques in this same disease (Kuo et al. 2001). Prions, the converted state of the normal cellular prion protein, PrPC, into the pathogenic form, PrPSc. on the other hand, are related to prion diseases such as transmissible spongiform encephalopathy (Dugger & Dickson, 2017), fatal familial insomnia, kuru, and sporadic and iatrogenic Creutzfeldt-Jacob disease (Ellison, 2013). TDP-43 is a protein that is normally involved in the repression of transcription, therefore participating in the modulation of RNA metabolism and gene splicing (Ratti and Buratti 2016). It has also been shown to be a major component in neuronal inclusions in Amyotrophic Lateral Sclerosis (ALS) and frontotemporal lobar degeneration associated with TDP-43 pathology (FTLD-TDP) (Neumann et al. 2006), while being also found in around 25-50% of Alzheimer's disease cases (Amador-Ortiz et al. 2007; Hu et al. 2008; Josephs et al. 2014)

Some of these protein aggregates cause damage to the membrane of organelles, like alpha-synuclein, inducing changes in membrane curvature and extensive tubulation and vesiculation, which can lead to cell death and, consequently, neurodegeneration

(Varkey et al. 2010). The accumulation of PrPC, for example, is associated with neuronal and synaptic loss, microvacuolation and gliosis. The aggregation of these different kinds of proteins has been shown to be often due to the activity of the transglutaminase enzyme, whose expression is normally upregulated in many of these diseases (Caccamo et al. 2010). Another important thing to note is the fact that these protein abnormalities can be present even before the clinical onset of the disease (Gibb and Lees 1988; Sparks et al.1994; Schmitt et al. 2000; Adler et al. 2010; Evidente et al. 2011; Frigerio et al. 2011; Milenkovic and Kovacs 2013; Dugger et al. 2014a).

The intrinsic mitochondrial apoptotic pathway is the main way through which neuron cell death most commonly happens. This pathway leads to the release of cytochrome c from the mitochondrial intermembrane space, which controls the activation of caspase-9, which is responsible for the activation of apoptosis. Besides this, mitochondria are also responsible for the formation of reactive oxygen species (ROS), which are normal by-products of the activity of the mitochondrial respiratory chain (DiMauro et al. 2008). Oxidative stress, the overproduction of ROS, is a central feature common to all neurodegenerative diseases (DiMauro et al. 2008) with neurons being particularly vulnerable to oxidative damage (Liu et al. 2017; Wang et al. 2017). Besides this, mitochondria are also involved in many functions that help maintain the cell alive, like calcium homeostasis, mitochondrial fission and fusion, which makes it so that mitochondrial disease can lead to neurodegeneration. This has been proven for Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis (Lin & Beal, 2006).

Damage to DNA is another mechanism through which neurodegeneration can occur. This can happen due to the action of ROS produced by oxidative metabolism, which when coupled with the gradual decline of DNA repair mechanisms caused by aging, can lead to an accumulation of DNA damage over time, leading to brain aging and, therefore, neurodegeneration. Defective DNA repair has been linked to many neurodegenerative diseases, like Alzheimer's, Parkinson's, amyotrophic lateral sclerosis, ataxia telangiectasia, Cockayne syndrome and xeroderma pigmentosum (Madabhushi et al 2014; Jeppesen et al. 2011).

Axonal modification and degeneration are also known to be involved in neurodegeneration, with disruptions of axonal transport being the cause of a degenerative pathway called the Wallerian-like degeneration (Coleman & Freeman, 2010).

From this, we can conclude that while most neurodegenerative diseases are normally defined by the accumulation of a specific protein and anatomic vulnerability, they share many different processes by which neurodegeneration ends up occurring, like the ones listed previously (Dugger & Dickson, 2017), and that more than one neurodegenerative disease process can be found in a single individual (Uchikado et al. 2006; Dugger et al. 2014b). Cross-sectional evaluations done postmortem have shown that many neurodegenerative diseases progress by stages, including Alzheimer's disease (Braak and Braak 1991; Thal et al. 2002), Parkinson's disease (PD) (Braak et al. 2003), dementia with Lewy bodies (DLB) (Kosaka et al. 1984), amyotrophic lateral sclerosis (ALS) (Brettschneider et al. 2013), FTLD-TDP (Brettschneider et al. 2014), and chronic traumatic encephalopathy (CTE) (McKee et al. 2013).

3| Alzheimer's Disease

Alzheimer's disease (AD) is a type of dementia that is normally characterized by cognitive and functional decline that worsens throughout its course, which is associated with age and ends up in death (Alzheimer's Association, 2019; Lopez et al. 2019). AD was first described in 1906 by Alois Alzheimer, based on his findings from one of his patients at the time (Moller and Graeber, 1998), and since then, many diagnostic criteria for this disease have been modernized and refined, through the use of biomarkers and the ability to identify and characterize the preclinical stages of AD (McKhann et al., 2011; Sperling et al., 2011; Jack et al., 2018; Lopez et al. 2019). One of the most defining breakthroughs that happened in the study of this disease was the description of the molecular identities of the substances that are now known to be involved in the

development of AD in the mid-1980s: beta-amyloid peptide and the hyperphosphorylated tau protein found in neurofibrillary tangles (Glenner and Wong, 1984a,b; Brion et al., 1985; Grundke-Iqbal et al., 1986; Kosik et al., 1986; Pollock et al., 1986; Lopez et al. 2019).

Most AD cases are sporadic, but mutations in three specific genes (the amyloid precursor protein (APP), the presenilin 1 (PSEN1) and presenilin 2 (PSEN2) genes) can cause a rare familial form of AD that causes symptoms to develop earlier than sporadic AD (between the ages of 30-50 years) (Bateman et al., 2010; Lane et al., 2018). On another hand, typical late-onset AD seems to be caused by both genetic and environmental factors, with the APOE gene and its three variants being the biggest risk factor to developing the disease (Lane et al., 2018). Other genetic risk factors have been identified as well, implicating inflammatory, cholesterol metabolism and endosomal vesicle recycling pathways, as well as microglial activation in response to amyloid deposition (Karch and Goate, 2015; Lane et al., 2018). Environmental risk factors include air pollution, diet, metals, infections, and many others that can contribute to the risk of developing AD by inducing oxidative stress and inflammation (Wainana et al., 2014; Grant et al., 2002; Breijyeh and Karaman, 2020).

AD is the type of neurodegenerative dementia that is most common in the United States and the world, and it has been shown that the prevalence of this disease increases with age: ~3% of people aged 65-75 are affected by the disease in the United States; of people 75-85, ~17% are affected and of people older than 84 years of age, around 32% have the disease (Alzheimer's Association, 2019; Babulal et al., 2019; Lopez et al. 2019). According to several studies, the people affected by AD are two-thirds female and one-third male, which can be explained due to genetic factors and the longer life expectancy of females (Lopez et al. 2019). It is also known that Hispanics and African Americans have one and a half times higher risk than Caucasians to develop AD (Lopez et al. 2019).

Alzheimer's disease is normally described as a person's slow, progressive cognitive decline with associated functional impact (Lopez et al. 2019). There can be an insidious onset of loss of episodic memory and difficulties in semantic memory (like

naming objects and people), progressive spatial and temporal disorientation, visuospatial deficits, and also language decline, with executive deficits manifesting early in the disease process (Lopez et al. 2019). Eventually, other deficits can also appear, including confusion, cognition fluctuations, anosognosia, serious lapses in judgment, disruptive behaviours, prosopagnosia and apraxia (Lopez et al. 2019). The appearance of functional difficulties in instrumental daily living tasks, that are not better explained by other changes in general health, are normally accepted as the tipping point from when mild cognitive impairment becomes dementia (Lopez et al. 2019). Neuropsychiatric and sleep changes can also accompany and exacerbate cognitive and functional deficits, with agitation, depression, and anxiety being normally noticed early in the disease's history and hallucinations and paranoid delusions starting to appear later on in the disease's process, with eventual worsening as time goes on (Lopez et al. 2019) Due to this, there is a necessity to evaluate for any changes in the patient's mood, sleep and behaviour, which can be done by using the many previously established and validated clinical scales that have been created to track and measure these kinds of symptoms (Yesavage et al., 1982; Cummings et al., 1994; Lesher and Berryhill, 1994; Loreck et al., 1994; Kaufer et al., 2000; Kroenke et al., 2001; Lopez et al. 2019). Another thing that's important to note is that comorbidities like psychiatric disorders, medical illnesses and medication use can be involved in the development of these kinds of changes (Lopez et al. 2019).

3.1| Mechanism of AD

The mechanism behind AD is still subject of discussion to this day, although the most prevalent hypothesis supported for it is called the amyloid cascade hypothesis, which centers around the accumulation of beta-amyloid plaques as the primary process that leads to the development of the disease (Selkoe, 2004; Querfurth and Laferla, 2010; Lopez et al. 2019). In addition, it has been shown that neuropil threads, dystrophic neurites, associated astrogliosis and microglial activation are often seen as well (Serrano-Pozo et al., 2011; Lane et al., 2018). Although the innate biological role of Aβ

is still not fully understood, it is suspected to be involved in the homeostatic scaling of synapses, immunity and the processing of lipids (Jang and Chung, 2016; Kumar et al., 2016; Bis et al., 2018; Kunkle et al., 2019; Lopez et al. 2019). In the healthy human brain, the amyloid precursor protein (APP) is produced by several types of cells before undergoing cleavage through two distinct pathways, the non-amyloidogenic pathway and the amyloidogenic pathway (Lopez et al. 2019). In the amyloidogenic pathway APP is cleaved by b-secretase, producing sAPPb and C99. C99 is then processed by g-secretase, resulting in the formation and secretion of amyloid-beta protein (Aβ) and other side products (Lopez et al. 2019). The regulation of either of these two pathways isn't understood completely, but it is generally accepted that the overproduction and/or reduced clearance of the normally soluble Aβ leads to their oligomerization, and subsequently leads to the formation of Aβ fibrils that then form the characteristic Aβ plaques present in the brain tissue of AD patients (Lopez et al. 2019).

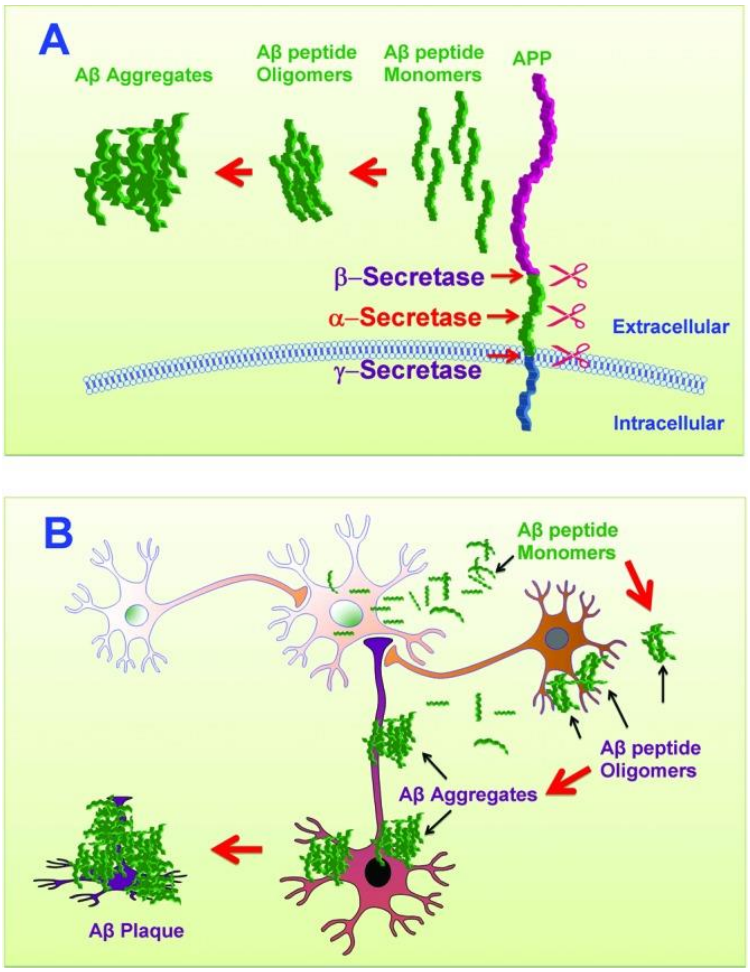

Figure 4: Simplified model of the amyloid cascade hypothesis and the role of Aβ in AD pathogenesis (Adapted from: Kung et al. 2012)

Studies have shown that both Aβ products are toxic, and they are thought to induce secondary or downstream events such as inflammation, oxidative stress, excitotoxicity and even the production of neurofibril tangles due to the induction of hyperphosphorylation in tau proteins (which has been shown to have a role in impairing signalling cascades, mitochondrial function, and axonal transport) (McLean et al., 1999; Harris et al., 1995; Lopez et al. 2019). All these processes cause eventual cell death and deficits in neurotransmission (especially affecting acetylcholinergic transmission), which leads to the development of some of the characteristic symptoms of AD (Francis et al., 1999; Lopez et al. 2019). Recent studies have pointed out that both Aβ and tau can

seemingly undergo refolding to achieve a “misfolded infectious state”, in a process that scientists have named templating, which enables them to induce self-propagating misfolding of endogenous proteins (Prusiner, 2012; Lopez et al. 2019).

The loss of synaptic plasticity and the neurodegeneration of synapses themselves are a focal point in terms of the clinical manifestations of AD (Lopez et al. 2019). The initial clinical characteristic of AD is the incapability of producing and storing new memories, which can be correlated to global changes in the number of synapses and postsynaptic receptors. Aβ is known to be the main cause of these changes, which leads to cognitive decline (DeKosky and Scheff, 1990; Dewar et al., 1991; Terry et al., 1991; Armstrong et al., 1994; Masliah et al., 1994; Ikonomovic et al., 1995; Armstrong and Ikonomovic, 1996; DeKosky et al., 1996; Koffie et al., 2009; Perez-Nievas et al., 2013; Boros et al., 2017; Lopez et al. 2019). The loss of postsynaptic receptors seems to be selective, leading to a loss of the mechanisms of storage of long-term memory, which might explain why normally implicit memory tends to be preserved throughout the disease’s course, comparatively to explicit memory (Kessels et al., 2011; Zhou et al., 2018; Lopez et al. 2019)

3.2| Pathophysiology

The spread of hyperphosphorylated tau proteins together with progressive aberrations leads to the formation of regional distributions of NFTs that have been previously described and divided into what is known as the Braak stages (Lopez et al. 2019). Hyperphosphorylated tau can be at first detected in the magnocellular nuclei of the basal forebrain, in the brain stem raphe system’s oral nuclei, and the locus coeruleus; however, the first NFTs have been shown to develop on the transentorhinal cortex (in what is described as Braak stage I) and in the entorhinal cortex itself (which is characterized as Braak stage II) (Lopez et al. 2019). Subsequently, NFTs then spread to the hippocampus (Braak stage III), into the superior temporal gyrus and the middle temporal convolution (Braak stage IV), and finally to the remainder of the cerebral cortex (Braak stages V and VI) (Lopez et al. 2019).

Cognitive impairment tends to appear when the disease reaches Braak stage III, worsening with the progression through stages, mostly due to loss of forebrain cholinergic neurons and loss of limbic and neocortical presynaptic cholinergic innervation caused by neurofibrillary degeneration (Braak et al., 2006; Braak and Del Tredici, 2015; Lopez et al. 2019). It's important to note though that even before measurable clinical deficits appear, other processes are already taking place during earlier stages of AD, such as up and downregulation of protein expression (with upwards to 900 genes being activated in the prefrontal cortex before the accumulation of any AD-related proteins) and also the appearance of neuritic amyloid plaques in the extracellular space, which can be quantified per microscopic view in the normally affected areas of the brain (superior and middle temporal gyri, middle frontal gyrus, and inferior parietal lobule) and also classified qualitatively based on how frequently they are observed in the brain (Bossers et al., 2010; Mirra et al., 1991; Lopez et al. 2019). Another thing to consider is the fact that biologically inert diffuse amyloid plaques also exist, which are normally also described qualitatively based on plaque density, using the same 100ff microscopic field of view (Lopez et al. 2019). Amyloid plaques are also normally described based on their distribution across brain regions, with phase 1 being correlated with their presence in the frontal, parietal, temporal, and occipital cortex while phase 5 correlates with their spread up to the brainstem and cerebellum (Thal et al., 2002; Lopez et al. 2019).

Due to the fact that other comorbid neuropathologies often accompany AD in its presentation, which are often common and age-related and can have a role on the onset of clinical dementia, the neuropathologic and assessment criteria for AD were revised and updated in 2012, so as to become more inclusive of the existence of these pathologies (Khachaturian, 1985; Mirra et al., 1991; Newell et al., 1999; Hyman et al., 2012; Montine et al., 2012; Robinson et al., 2018a,b; Nelson et al., 2019; Lopez et al. 2019). The most important of these pathologies are the neurovascular dysfunction and blood-brain barrier breakdown that can accompany tau-related diseases; Lewy bodies and other protein deposits (Kisler et al., 2017; Lopez et al. 2019). The most important aspect to retain though is that the neuron and synapse lost and the vascular and

metabolic dysfunction together with inflammatory changes and neurologic comorbidities that appear are what underlies the preclinical and clinical stages of AD (Lopez et al., 2019).

3.3| AD Diagnosis

The first step in diagnosing AD is to perform a comprehensive physical and neurologic examination during the first visit, which should include the measuring of vital signs, weight and BMI, the assessment of pain, physical signs of end-organ failure, delirium and abuse, neglect or falls (Lopez et al., 2019).

The four-question Alzheimer's Questionnaire has high discriminatory power and screening tests like MMSE and the Montreal Cognitive Assessment (MoCA) are useful and used to evaluate and track the progression of cognitive decline, and they can be augmented as necessary if any unique deficits are observed in specific cognitive domains (Folstein et al., 1975; Nasreddine et al., 2005; Malek-Ahmadi et al., 2012; Lopez et al., 2019). The MoCA screening test is subdivided into different sections that test for impairment in specific cognitive domains, including visual-spatial/executive, naming and language, different types of memory, attention, abstraction, and orientation (Lopez et al., 2019). Other screening tests are also available like the General Practitioner Assessment of Cognition (GPCOG), the Mini-Cog and the Memory Impairment Screen, which are all recommended by the Alzheimer's Association (Brodaty et al., 2002, 2004; Borson et al., 2003; Lopez et al., 2019). Especially when dealing with patients with difficulties in naming or language, the examiner might feel the need to explore these domains in more detail, which can be possible to do using the Boston Naming Test or the "Cookie Theft Picture" from the Boston Diagnostic Aphasia Examination (Roth, 2011; Lopez et al., 2019). Visual-spatial impairment can also be tested through the use of tests like the simple line bisection task (Valenstein, 2012; Lopez et al., 2019), while other tests for praxis can also be relevant to test in patients with language or visual special deficits (Lopez et al., 2019).

When patient cooperation is impossible, assessment through caregiver questionnaires can help solve the issue, which includes the Ascertain Dementia 8, the GPCOG's informant interview section, and the Informant Questionnaire of the Cognitive Decline in the Elderly short form (Brodaty et al., 2002, 2004; Jorm, 2004; Galvin et al., 2005, 2006; Ding et al., 2018; Chen et al., 2018a,b; Lopez et al., 2019). Furthermore, as disease progression makes cognitive testing more difficult and unreliable, the use of batteries of tests like the Severe Impairment Battery can be useful as well (Panisset et al., 1994; Lopez et al., 2019). Finally, extensive neurocognitive testing is indicated in more extreme cases where a confident diagnosis can't be achieved through routine history and bedside mental status examination (Lopez et al., 2019).

In terms of biomarkers, it is important to consider that the clinical diagnosis of AD does not require the measuring of biomarkers, with the clinical profile and the absence of other contributors or causes being sufficient to make a probable diagnosis (Lopez et al., 2019). However, biomarkers may have practical importance to support clinical evidence when the presentation of the disease is atypical or when diagnostic criteria for other etiologies are present (Lopez et al., 2019). In these cases, the normal approach is to start by doing an MRI and FDG-PET in order to see if unique patterns of hippocampal and/or parietal atrophy and lateral and mesial temporoparietal hypometabolism can be observed, since these manifestations tend to be typical of AD, leading to alternative etiologies being less likely (Lopez et al., 2019). Afterwards, depending on what resources are available, an evaluation of the CSF or an amyloid PET can be performed so as to confirm the presence of AD (Jack et al., 2008; Brewer et al., 2009; Lopez et al., 2019). Amyloid PET allows the confirmation of the presence of fibrillar amyloid plaques, and while a positive test doesn't allow for absolute certainty for the diagnosis of AD, a negative result rules out AD and is indicative that another etiology is responsible for the patient's dementia (Lopez et al., 2019). Meanwhile, CSF evaluation can be used to determine the concentration of Ab in the CSF, total and phosphorylated tau and to exclude other etiologies of dementia when an atypical clinical presentation is present (Herukka et al., 2017; Simonsen et al., 2017; Lee et al., 2019; Lopez et al., 2019). Of note is that it is now possible to detect early biomarkers of the breakdown of the

blood brain barrier and of capillary damage that are detectable before amyloid or tau disease pathology onset, with vascular dysfunction biomarkers being likely to be incorporated in the near future into the biologic definition of AD (Nation et al., 2019; Sweeney et al., 2019; Lopez et al., 2019).

Biomarkers that could follow the onset and course of the cognitive decline that is characteristic of AD dementia while independent of the primary pathology are still not available, although they are being currently researched actively (Koffie et al., 2009; Kay et al., 2013; Perez-Nievas et al., 2013; Boros et al., 2017; Xiao et al., 2017; Arenaza-Urquijo and Vemuri, 2018; Chen et al., 2018a,b; Lopez et al., 2019). Biomarkers of "synaptic plasticity" like these, could potentially inform clinical trials and help with prevention and treatment strategies (Lopez et al., 2019).

3.4| Symptomatic treatment

It is important to note that, so far, the only pharmacological intervention that exists for Alzheimer's disease is symptomatic and not curative (Lopez et al., 2019). The first-line drugs used in the symptomatic treatment of Alzheimer's disease are the cholinesterase inhibitors, which are indicated for early and moderately advanced stages of the disease (Lopez et al., 2019). The choice of the specific anticholinesterase drug that is chosen is based on convenience to the patient and the side-effect profile of each drug (Lopez et al., 2019). Cholinesterase Inhibitors are also used off-label for mixed disease presentation, Lewis Bodies Dementia and vascular cognitive impairment, although they are not normally indicated for the treatment of mild cognitive impairment even if sometimes the blurred line between dementia and this pathology may justify its eventual usage (Lopez et al., 2019). Memantine can be utilized as a sole treatment or in conjunction with other cholinesterase inhibitors in moderate and severe AD, being considered first-line in severe disease since it can help treat behavioural changes (Lopez et al., 2019).

In the management of mood, behavioural and sleep manifestations of AD, Selective Serotonin Reuptake Inhibitors (SSRIs) and even certain tricyclic

antidepressants are indicated, with the use of pure SSRIs like escitalopram being encouraged as a first-line treatment (Lopez et al., 2019). It is important to note that other drugs like trazodone and mirtazapine might also be chosen if mood and sleeping difficulties are present, due to their sedative properties (Lopez et al., 2019). Drugs with strong anticholinergic effects should be avoided (American Geriatrics Society, 2015), as should neuroleptics, antipsychotics and benzodiazepines (with the exceptions of clonazepam for rapid eye movement sleep behaviour disorder) (Lopez et al., 2019).

Recently, one new drug was approved by the FDA for the treatment of AD: Biogen's aducanumab. This drug was approved through the FDA's rapid drug approval pathway, due to the potential benefit it could bring with Aβ plaque removal (Walsh et al., 2021). While the approval of this drug itself is controversial, due to circumstantial evidence of it's eventual effectiveness, taken together, these findings emphasize the importance of investigating Aβ toxicity and the need for better therapeutic targets.

4| Role of astrocytes in AD pathology

Studies show that the genes that are majorly associated with the risk of developing AD are expressed in astrocytes, including clusterin (ApoJ), sortilin-related receptor 1, fermitin family member 2, and ApoE, which supports the fact that this type of glial cell plays a critical role in the pathogenesis of AD (Arranz and De Strooper, 2019). This is further supported by the fact that astrocytes undergo morphological, molecular, and functional changes in AD, which has been shown both in experiments using mouse models with mutated genes and also in brain samples of patients with the disease and can even be observed before the appearance of amyloid plaques (Orre et al., 2014; Rodriguez-Arellano et al., 2016; Verkhratsky et al., 2016; Liddelow et al., 2017a; Arranz and De Strooper, 2019). Astrocytes that are hypertrophic and reactive are located close to amyloid plaques, and while they do not overlap with neighbouring astrocytes, they have been shown to produce spontaneous calcium oscillations and abnormal intercellular calcium waves, which seems to contribute to the neuroinflammatory

processes of AD (Orre et al., 2014; Verkhratsky et al., 2016; Arranz and De Strooper, 2019, Habib et al., 2020). Besides this, there is data from mouse studies that seem to indicate that astrocytes are promotors of cell death in AD after being instigated by microglia: activated microglia secrete interleukin-1α (IL-1α), tumour necrosis factor α (TNFα), and complement component 1q (C1q), leading to the induction of the A1 neurotoxic astrocyte phenotype, which in turn upregulate the expression of genes of the complement cascade and also seems to lead to the release of neurotoxic substances (Hong et al., 2016; Sekar et al., 2016; Liddelow et al., 2017a; Liddelow et al., 2017b; Arranz and De Strooper, 2019).

In physiological conditions, astrocytes are the main type of cells in the brain that express ApoE, expressing various types of this transport protein, especially ApoE3 and ApoE4 (Zhao et al., 2017; Arranz and De Strooper, 2019). Astrocytes expressing ApoE4 have been shown to have an impaired amyloid-β uptake and cholesterol accumulation in comparison to ApoE3 expressing astrocytes, which in turn seems to lead to impaired autophagy capabilities and excessive endosomal acidification (Simonovitch et al., 2016; Lin et al., 2018; Prasad et al., 2018; Arranz and De Strooper, 2019). ApoE expression in astrocytes is also seemingly linked to the initial seeding of amyloid deposits, with ApoE4 having a more prominent role in this than ApoE3 astrocytes. There is also evidence that ApoE also affects plaque size and neuritic dystrophy, while not affecting total amyloid load (Huynh et al., 2017; Liu et al., 2017; Arranz and De Strooper, 2019). Astrocytic ApoE4 is also involved in the activation of the cyclophilin A-NF- κB metalloproteinase 9 pathway, which leads to an increase in both cyclophilin A and metalloproteinase 9 concentrations in the brain and CSF and results in an increase of the blood-brain barrier's permeability (Sweeney et al., 2016; Sweeney et al., 2018; Arranz and De Strooper, 2019). This correlates with pericyte degeneration and the breakdown of the blood-brain barrier in brain tissue samples obtained from AD patients, which then contributes to proinflammatory responses and neurodegeneration (Sweeney et al., 2016; Sweeney et al., 2018; Arranz and De Strooper, 2019). It has also been shown in mouse models that amyloid-β itself can activate the NFκB pathway in astroglia, which can cause astrocytes to display the A1-phenotype and resulting in the release of C3 into the extracellular

space, which binds to neuronal C3aR receptors and disrupts dendritic morphology and network function (Lian et al., 2015; Lian et al., 2016; Arranz and De Strooper, 2019).

Despite all this, there is also evidence that the A2 astrocyte phenotype can have a protective role in AD, which seemingly indicates that not all amyloid-β-activated astrocytes are detrimental (Lian et al., 2016; Arranz and De Strooper, 2019). A2 astrocytes secrete neurotrophic factors that promote neuronal survival and growth as well as thrombospondins involved in synapse repair (Liddelow et al., 2017; Arranz and De Strooper, 2019). However, the secretion of neurotrophic transforming growth factor has been shown to both enhance microglial uptake of amyloid-β and protect neurons from amyloid-β toxicity but also to lead to neuronal signalling that promotes amyloid precursor protein transcription and amyloid-β production (Lian et al., 2016; Diniz et al., 2017; Arranz and De Strooper, 2019). It has also been shown in both AD patients and mouse models that reactive astrocytes surrounding amyloid-β plaques have phagocytic activity and engulf neuritic dystrophies (Gomez-Arboledas et al., 2018; Arranz and De Strooper, 2019).

4.1| Effect on gliotransmission by Alzheimer's disease

Although the role of astrocytes in neurodegenerative diseases has not always been accepted, this paradigm has changed in recent years due to the acceptance of astrocytes as active contributors to homeostasis of the brain's function and evidence that the disruption of these cells' function being a critical contributor to the pathology of most neurodegenerative diseases, including AD (Nanclares et al., 2021). Many studies have shown that Ca^{2+} signalling is affected by exposure of astrocytes to Aβ, leading to increases in intracellular Ca^{2+} both in mouse models and cell cultures of the disease (Chow et al., 2010; Kuchibhotla et al., 2009; Takano et al., 2007). On another hand, Furman et al in 2012 showed that the blocking of Ca^{2+}-dependent protein phosphatase calcineurin (an enzyme involved in astrocyte activation) in APP/PS1 AD mouse models

could actually improve cognitive and synaptic function, reduce glial cell activation and lower amyloid levels (Furman et al., 2012).

The homeostasis of glutamate by astrocytes is another factor that seems to be affected due to Aβ exposure: studies using APP/PS1 AD mouse models have showed that Aβ plaques lead to regional reduction and dysfunction of GLT-1, which affects the clearance rates of glutamate by astrocytes (Stenovec et al., 2016; Hoshino et al., 2017; Stevenson et al., 2020). Besides this, there has also been shown that there's a reduction of glutamate transporters EAAT1 and EAAT2 in early AD progression, which was associated with cognitive decline (Masliah et al., 1996). Moreover, the presence of Aβ itself seems to potentiate the release of glutamate by astrocytes, which triggers the activation of eNMDAR and leads to neuronal cell death, with resulting synaptic loss (Talantova et al., 2013). All this seems to point to the fact that the dysregulation of synaptic function, cognition and plasticity that characterizes AD might be caused mainly by an increase of glutamate release and a decrease in the reuptake of this gliotransmitter, with astrocytes being the key for these mechanisms.

Although there are several studies that have tried to ascertain what kind of role D-serine might have in AD pathophysiology (Madeira et al., 2015; Balu et al., 2019; Nuzzo et al., 2020), the evidence is still not clear. There seems to be some evidence that an increase of D-serine levels and the consequent NMDAR hyperfunction might be a contributor to both excitotoxicity and also memory impairment in AD (Balu et al., 2019). On another hand, there is also evidence that D-serine might actually have a neuroprotective role, by activating sNMDAR and inhibiting the JNK pathway that promotes apoptosis (H. Liu et al., 2020).

Despite this, there is enough evidence to accept the fact that Aβ has a profound effect over Ca^{2+} signalling performed by astrocytes, which leads to a dysregulation of gliotransmission, which seems to be an important factor behind many of the hallmark manifestations of AD, due to the resulting neuronal loss.

5| Future prospects

First of all, it is important to take into account that the fact that astrocytes can have different reactive phenotypes brings up several possibilities in terms of the development of new therapies not only for the treatment of Alzheimer's disease but also other neurodegenerative diseases, like the development of therapies that block the formation of A1 phenotype neurotoxic astrocytes, for example (Arranz and De Strooper, 2019). So far, the most promising approaches seem to be those that block specific neuroinflammatory factors that are secreted by microglia (like TNFα, IL1α, and C1q) or that effectively block the activation of these cells (Arranz and De Strooper, 2019). TNFα seems to be a potential candidate to be a good therapeutic target, seeing as there are studies that indicate that elevated serum concentrations of this neuroinflammatory factor are present in AD patients compared to controls (Ekert et al., 2018; Arranz and De Strooper, 2019). Due to this, the usage of TNFα antagonism to block the conversion of astrocytes to their A1 neurotoxic phenotype might help ameliorate inflammation in AD patients (Arranz and De Strooper, 2019). Some studies have been conducted utilizing etanercept, a TNFα inhibitor that is normally used in the treatment of rheumatoid arthritis (RA), but while at a first glance the therapy using this drug seemed to reduce the relative risk of developing AD in patients with RA in comparison to healthy untreated controls in a large nested case-control, results were not conclusive in another posterior phase 2 trial where patients with AD were injected subcutaneously with etanercept (Chou et al., 2016; Decourt et al., 2017; Arranz and De Strooper, 2019).

Other drugs that are normally used for the treatment of RA and sepsis have also been considered for the treatment of AD, like anakinra (an IL1α recombinant antagonist) and C1q inhibition antibodies, but no clinical trials of these drugs are reported to be ongoing (Goldbach-Mansky et al., 2009; Liddelow et al., 2017; Arranz and De Strooper, 2019). Another potential target could be C3 or its receptor C3aR, seeing as this substance is secreted by astrocytes activated by NF-κB (Lian et al., 2015; Arranz and De Strooper, 2019). Information obtained from cell cultures and mouse studies seem to indicate that the use of a C3aR antagonist or a genetic deletion of this receptor seems

to restore cognitive deficits in transgenic mice (Lian et al., 2015; Lian et al., 2016; Arranz and De Strooper, 2019). NLY01, a long-acting glucagon-like peptide-1 receptor (GLP1R) agonist is another potential drug that might be beneficial, seeing as in studies with mice it was shown to block the activation of microglia and the subsequent shift of astrocytes into their A1 neurotoxic phenotype (Yun et al., 2018; Arranz and De Strooper, 2019). A study using P2Y1 antagonists in a mouse model of AD, being P2Y1 strongly expressed in reactive astrocytes present near amyloid plaques, also showed positive results, with normalization of the neuronal-astroglial network activity, the restoration of structural and functional synaptic integrity, the reduction of neuritic dystrophy and the attenuation of cognitive decline (Reichenbach et al., 2018; Arranz and De Strooper, 2019).

D-serine is another potential pharmacological target to take into account, due to underlying evidence that this gliotransmitter might be able to promote neuroprotection while maintaining normal neuronal function through the activation of sNMDAR (H. Liu et al., 2020). As mentioned above though, there is still some controversial opinions on the matter due to the potential role this gliotransmitter might also have in potentiating excitotoxicity and neuronal death (Balu et al., 2019), which is why more studies are needed to clarify these aspects and ascertain the actual potential of D-serine as a therapeutic target for Alzheimer's.

Another field of research that has importance is the discovery and implementation of specific biomarkers and neuroimaging to analyse pre-symptomatic pathological processes present in astroglia (Arranz and De Strooper, 2019). An example of this is the monoamine oxidase B activity in astrocytes, which can be detected and followed by PET scan and that have been shown to be found in early stages of AD, with especially high signalling during prodromal stages of the disease (Rodriguez-Vieitez et al., 2016; Arranz and De Strooper, 2019).

6| Conclusions and future directions

There are strong insights that glial cells play a major role in the pathogenesis of AD, with astrocytes, who are normally essential for brain homeostasis, survival and protection of neurons, becoming reactive and ending up causing neuroinflammation and neurodegeneration (Liddelow et al., 2017; Yun et al., 2018; Rothhammer et al., 2018; Ouali Alami et al., 2018; Arranz and De Strooper, 2019). Due to this, it's important to try to do more and better studies to understand how astrocytes work and react in different conditions, so that in the future it will be possible to relate different states of astrocyte reactivity to different stages of AD (Arranz and De Strooper, 2019).

There is still one thing that is important to solve though, which are the differences between mouse and human astroglia (Arranz and De Strooper, 2019). This problem might be possible to solve using iPSC-derived astrocytes in vitro or transplanted in vivo to create chimeric mice or even maybe using single-cell transcriptomics to isolate nuclei and even cells from autopsied or frozen brain samples (Arranz and De Strooper, 2019). This could maybe open up the possibilities of discovering new biomarkers or drug targets for AD diagnosis and treatment (Arranz and De Strooper, 2019).

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