



Involvement of Astrocytes in Alzheimer's Disease from a Neuroinflammatory and Oxidative Stress Perspective

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Received: 26 September 2017

Accepted: 06 December 2017

Published: 19 December 2017

Citation:

González-Reyes RE, Nava-Mesa MO, Vargas-Sánchez K, Ariza-Salamanca D and Mora-Muñoz L (2017) Involvement of Astrocytes in Alzheimer's Disease from a Neuroinflammatory and Oxidative Stress Perspective. *Front. Mol. Neurosci.* 10:427. doi: 10.3389/fnmol.2017.00427

Alzheimer disease (AD) is a frequent and devastating neurodegenerative disease in humans, but still no curative treatment has been developed. Although many explicative theories have been proposed, precise pathophysiological mechanisms are unknown. Due to the importance of astrocytes in brain homeostasis they have become interesting targets for the study of AD. Changes in astrocyte function have been observed in brains from individuals with AD, as well as in AD *in vitro* and *in vivo* animal models. The presence of amyloid beta (A β) has been shown to disrupt gliotransmission, neurotransmitter uptake, and alter calcium signaling in astrocytes. Furthermore, astrocytes express apolipoprotein E and are involved in the production, degradation and removal of A β . As well, changes in astrocytes that precede other pathological characteristics observed in AD, point to an early contribution of astroglia in this disease. Astrocytes participate in the inflammatory/immune responses of the central nervous system. The presence of A β activates different cell receptors and intracellular signaling pathways, mainly the advanced glycation end products receptor/nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway, responsible for the transcription of pro-inflammatory cytokines and chemokines in astrocytes. The release of these pro-inflammatory agents may induce cellular damage or even stimulate the production of A β in astrocytes. Additionally, A β induces the appearance of oxidative stress (OS) and production of reactive oxygen species and reactive nitrogen species in astrocytes, affecting among others, intracellular calcium levels, NADPH oxidase (NOX), NF- κ B signaling, glutamate uptake (increasing the risk of excitotoxicity) and mitochondrial function. Excessive neuroinflammation and OS are observed in AD, and astrocytes seem to be involved in both. The A β /NF- κ B interaction in astrocytes may play a central role in these inflammatory and OS changes present in AD. In this paper, we also discuss therapeutic measures highlighting the importance of astrocytes in AD pathology. Several new therapeutic approaches involving phenols (curcumin), phytoestrogens (genistein), neurosteroids and other natural phytochemicals have been explored in astrocytes, obtaining some promising results regarding cognitive improvements and attenuation of neuroinflammation. Novel strategies comprising astrocytes and aimed to

reduce OS in AD have also been proposed. These include estrogen receptor agonists (pelargonidin), *Bambusae concretio Salicea*, Monascin, and various antioxidants such as resveratrol, tocotrienol, anthocyanins, and epicatechin, showing beneficial effects in AD models.

Keywords: astrocytes, Alzheimer's disease, neuroinflammation, oxidative stress, NF- κ B pathway, neurodegeneration

INTRODUCTION

The loss of cognitive abilities induced by the development of dementia represents one of the main pathological burdens in humans, critically interfering with social and occupational activities. According to the World Alzheimer Report, over 46 million people live with dementia worldwide, totaling an estimated cost of US \$818 billion in 2015, expecting to rise up to \$1 trillion by 2018 (Prince et al., 2015). The elevated economic and social impact of dementia has been considered as a public health priority by the World Health Organization (Frankish and Horton, 2017). Many types of dementia with varied pathophysiological mechanisms have been described, but the most frequent in humans is AD accounting for 50–70% of all cases (Querfurth and LaFerla, 2010). Characteristically, AD has been divided in early-onset AD (<65 years) and late-onset AD, with the latter representing around 90% of AD-affected individuals (Mendez, 2017; Pierce et al., 2017). The development of early-onset AD has been related to an altered genetic background, explained primarily by autosomal dominant mutations in *APP* (MIM #104760), *Presenilin 1 (PSEN1)* (MIM #104311), and *Presenilin 2 (PSEN2)* (MIM #600759) genes (Lanoiselée et al., 2017). Whereas a complete explanation for the development of late-onset AD (also commonly referred to as sporadic AD) remains obscure, despite the many risk factors associated with this pathology. Among these factors are included: genetic, such as the presence of the APOE ϵ 4 allele, environmental, and several modifiable lifestyle factors (Killin et al., 2016; Van Cauwenbergh et al., 2016; Vos et al., 2017).

Abbreviations: A β , amyloid beta; AD, Alzheimer's disease; AGE, advanced glycation end products; Aldh1L1, aldehyde dehydrogenase 1 family member L1; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APP, amyloid precursor protein; ApoE, apolipoprotein E; BACE-1, beta-site APP cleaving enzyme 1; BBB, blood-brain barrier; CaN, calcineurin; CaSR, calcium sensing receptor; CD, cluster of differentiation; CNS, central nervous system; COX, cyclooxygenase; ECE, endothelin-converting enzyme; ERK, extracellular regulated kinase; GABA, gamma-aminobutyric acid; GFAP, glial fibrillary acid protein; GLAST, glutamate aspartate transporter; GLT-1, glutamate transporter 1; GPX, glutathione peroxidase; GSH, glutathione; HMGB1, high mobility group box-1; IDE, insulin degrading enzyme; IKK α , NF- κ B inhibitor alpha; IKK, I κ B kinase; IL, interleukin; iNOS, inducible nitric oxide synthase; IR, insulin receptor; INF, interferon; JNK, c-Jun N-terminal kinase; MAO, monoamine oxidase; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; nAChR, nicotinic acetylcholine receptor; NADH, reduced nicotinamide-adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate; NEMO, NF- κ B essential modulator; NEP, neprilysin; NFAT, nuclear factor of activated T-cells; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; NMDA, N-methyl-D-aspartate; NO, nitric oxide; NOS, nitric oxide synthase; 8-OHG, 8-hydroxyguanosine; OS, oxidative stress; PI3K, phosphoinositide 3-kinase; PPAR γ , peroxisome proliferator-activated receptor gamma; RAGE, advanced glycation end products receptor; RNS, reactive nitrogen species; ROS, reactive

The main pathological hallmarks of AD are the presence of extracellular A β plaques, intraneuronal neurofibrillary tangles primarily composed of hyperphosphorylated tau, and brain atrophy, together with increased brain neuroinflammation (Raskin et al., 2015; Bronzuoli et al., 2016). Although many theories have been proposed to explain the pathogenesis of AD, the most widely accepted is the amyloid hypothesis, which states that A β dyshomeostasis is responsible for the cognitive phenotype of the disease, acting upstream and contributing to other molecular and cellular alterations observed in this condition (Selkoe and Hardy, 2016). A β peptide is obtained from the serial cleavage of APP, first through the action of BACE-1 also referred to as beta-secretase, and posteriorly through the gamma-secretase complex (Carroll and Li, 2016; Yan, 2017). The gamma-secretase complex, which also acts on the notch pathway, is composed of four subunits: presenilin (1 or 2), nicastrin, anterior pharynx-defective 1 (APH-1), and presenilin enhancer 2 (PEN2); with presenilin being the most actively studied and related to AD, as it contains the catalytic subunit of the complex (Ahn et al., 2010). Alterations in the cleaving process of APP produce abnormal lengthy species of the A β peptide which are deleterious to the brain cellular environment. These A β species have been reported to exhibit different profiles of toxicity, and among them, the soluble forms seem to be more neurotoxic than the fibrillary (aggregated) forms. In particular, the oligomeric form of the soluble A β _{1–42} is considered to be highly harmful (Wang Z.-X. et al., 2016).

The pathological study of brains from individuals with AD has revealed the presence of both neuroinflammation and OS (Lue et al., 1996; Ansari and Scheff, 2010). The precise mechanistic basis leading to the development of these changes in AD is not clear, and the debate of whether they are a causative factor or a consequence of the disease is still open. Despite the discussion, accruing evidence support a direct relationship between A β abnormal production and the development and/or maintenance of neuroinflammation and OS (Guerriero et al., 2016).

Plenty receptors and carriers have been reported to interact with the different presentations of A β , although it seems that depending on the structure of A β (monomer, oligomer, fibrillary), some promote clearance or degradation while others mediate the neurotoxic effects through uptake and accumulation (Jarosz-Griffiths et al., 2016). A β interacts and binds to several cellular-expressed pattern recognition receptors in astrocytes

oxygen species; SEC-R, serpin-enzyme complex receptor; SOD, superoxide dismutase; TGF- β , transforming growth factor beta; TLR, Toll-like receptor; TNF α , tumoral necrosis factor-alpha; TRAF, tumor necrosis receptor-associated factor; TREM2, triggering receptor expressed on myeloid cells 2.

and microglia, initiating an innate immune response (Minter et al., 2016). Accordingly, components of innate immunity and complement cascade have been considered risk factors for the development of AD and have been associated with abnormal clearing or deposition of A β ; in particular, variants in the genes complement receptor 1 (CR1) (Zhu et al., 2015), CD33 (Walker et al., 2015), and TREM2 (Yeh et al., 2016). Also, it has been shown that A β species, such as A β _{1–42}, are able to induce the release of several proinflammatory cytokines and agents, including IL-1 β , IL-6, NO, and TNF α , from glial cells (Lindberg et al., 2005; Hou et al., 2011). The precise intracellular signaling pathways involved in the proinflammatory and OS responses in neuronal and non-neuronal cells in AD are still not clear, although the NF- κ B pathway has been reported to become activated in both settings (Shi et al., 2016).

Astrocytes are important CNS resident cells involved in numerous physiological aspects. Similar to neurons, astrocytes represent a heterogeneous population of cells depicting diverse functional and morphological characteristics (Ben Haim and Rowitch, 2017). Astrocytes express several markers that allow them to be distinguished from neurons and other glial cells, including GFAP, calcium-binding protein S100B, glutamine synthetase, and Aldh1L1 (Sofroniew and Vinters, 2010). Astrocytes are key for the maintenance of homeostatic balance and participate in processes such as neurotransmitter uptake and recycling, gliotransmitter release, neuroenergetics, inflammation, modulation of synaptic activity, ionic balance, and maintenance of BBB, among others (Magistretti and Allaman, 2015; Iglesias et al., 2017; Vasile et al., 2017). Precisely, due to this wide array of functional properties, astrocytes have become interesting targets for the study and treatment of numerous brain pathologies. In AD, several reports have shown that astrocytes contribute to cellular and functional degeneration, disrupting glial–neuronal and glial–vascular signaling (Acosta et al., 2017).

The aim of this paper is to review the relevant aspects concerning a possible role of astrocytes in the neuroinflammatory and OS changes observed in AD. As well, we will discuss novel neuroprotective and therapeutic measures highlighting the importance of astrocytes in AD pathology.

ASTROCYTES AND ALZHEIMER'S DISEASE

Different studies have shown that the cooperative activity between glia and neurons results in the modulation of cognitive functions (Perea et al., 2009; Fields et al., 2014). Neuron–glial interactions actively control synaptic plasticity and neurotransmission. The concept of “tripartite synapse” refers to this cellular network involving both presynaptic and postsynaptic neurons, as well as astrocytes (Araque et al., 1999; Perea et al., 2009). Numerous gliotransmitters released from astrocytes control synaptic plasticity in different brain structures (Yang et al., 2003; Pascual et al., 2005; Panatier et al., 2006) such as cortex (Ding et al., 2007) and hippocampus (Araque et al., 1998; Jourdain et al., 2007), and are involved in the modulation of memory and learning processes. The interruption of astrocyte's

functions and hence in glia transmission, may result in different neuropsychiatric disorders (Rajkowska et al., 1999; Cohen-Gadol et al., 2004; Fellin et al., 2004; Webster et al., 2005), as well as neurodegenerative diseases, including AD (Forman et al., 2005; Halassa et al., 2007).

Calcium Dysregulation

A pathological increase in the amount of A β can induce functional and morphological changes in glial cells, including calcium dysregulation. In fact, microglia and astrocytes are activated close to senile plaques to internalize and break down A β (Mohamed and Posse de Chaves, 2011). This cellular activation may result in an inflammatory response and OS, playing a dual role in the pathophysiology of AD with both detrimental and neuroprotective results. Inflammatory mediators (i.e., bradykinin) may increase intracellular calcium concentration via nicotinic receptors and PI3K–Akt pathway in cultured astrocytes (Makitani et al., 2017). Tau has also been connected with astrocytes in AD, as A β was shown to bind the CaSR in human astrocytes, activating intracellular signaling which induced the production and release of phosphorylated Tau (Chiarini et al., 2017).

Amyloid beta has been shown to disrupt gliotransmission by enhancing calcium signaling in astrocytes (Lee et al., 2014). This calcium/gliotransmission alteration could underlie an important role of astrocytes in AD pathology. Actually, astrocytic calcium levels are abnormal in several models of AD as both acute and chronic exposure to A β elevates baseline calcium levels in cultured astrocytes (Haughey and Mattson, 2003; Alberdi et al., 2013; Lim et al., 2013). This calcium is partially released from intracellular sources such as the endoplasmic reticulum (Toivari et al., 2011). In addition, A β interacts with several types of surface receptors in astrocytes which leads to calcium entry, including purinergic receptor P2Y1 (Delekate et al., 2014), nicotinic receptors (α 7-nAChRs) (Xiu et al., 2005; Lee et al., 2014), and glutamate metabotropic receptor mGluR5 (Grolla et al., 2013; Ronco et al., 2014). For instance, hippocampal astrocytes exposed to A β increased the frequency of NMDA receptor-mediated slow inward currents, together with calcium elevations mediated through α 7nAChR activation (Pirttimaki et al., 2013). A β -induced dysfunction of NMDA receptors in astrocytes disrupts neuron–glial signal transmission with dramatic consequences on neuronal homeostasis, synaptic transmission, and plasticity. Therefore, neurotoxicity and selective neurodegeneration may be explained by A β simultaneous interaction with several receptors and neurotransmitter systems in the context of astrocyte calcium dysregulation.

Glutamatergic Dysfunction and Excitotoxicity

In AD, it has been shown that A β can interrupt glutamate uptake capacity and astrocytic calcium signaling (Vincent et al., 2010; Matos et al., 2012). Also, an increase in the expression of astrocytic Tau from aged transgenic animals leads to a decline in GLT activity and therefore in subsequent

neurodegeneration (Komori, 1999; Dabir et al., 2004). Some studies have demonstrated in *ex vivo* astrocyte preparations that A β _{1–42} decreases the expression of GLT-1 and GLAST, two major GLTs in astroglia, via adenosine A2A receptors (de Vivo et al., 2010; Matos et al., 2012). Therefore, disruption in the clearance of excitatory neurotransmitters and increased levels of A β and Tau from astrocytes seem to be involved in the neuronal excitotoxicity observed in AD.

Glutamate NMDA and AMPA receptors have been related to the physiopathology of AD (Parameshwaran et al., 2008). Different studies have identified the expression of functional NMDA receptors in astrocytes (Kommers et al., 2002; Lalo et al., 2006) involved in cerebral vasodilatation, synaptic transmission, and neuronal–glial signaling (Verkhatsky and Kirchhoff, 2007; Palygin et al., 2010; Parfenova et al., 2012). Hence, A β -induced dysfunction in the expression and function of glutamate receptors in astrocytes, mainly in NMDA receptors, can interfere with neuronal–glial communication (Mota et al., 2014). The cellular excitotoxicity produced by the excessive stimulation of NMDA receptors in neurons and astrocytes has been shown to be reduced with the use of MK801 and memantine (NMDA receptor antagonists) (Lee et al., 2010). Furthermore, due its possible therapeutic role in neurodegenerative diseases including AD, a recent antagonist (UBP141) with preferential effects on astroglial NMDA receptors has been developed (Palygin et al., 2010, 2011). A better comprehension of the differences between neuronal and glial NMDA receptors may provide key elements for the development of novel therapeutics which primarily or selectively target astrocytic function. As well, A β can induce glutamate release from astrocytes resulting in an extrasynaptic activation of NMDA receptors. In this case, nitromemantine, which selectively inhibits extrasynaptic NMDA receptors, may protect against A β -induced synaptic dysfunction in the hippocampus (Talentova et al., 2013). Additionally, nitromemantine may prevent the synapse-destroying effects of A β / α 7-nAChR signaling (Dal Prà et al., 2015).

Therefore, using astrocytic signaling as a possible target for drug development may have a therapeutic function in AD's prevention and control. The antiepileptic drug levetiracetam has shown to reverse synaptic dysfunction as well as memory and learning deficits in human APP (hAPP) transgenic mice (Sanchez et al., 2012). Moreover, a retrospective observational study has shown clinical benefits of levetiracetam in early AD (Vossel et al., 2013). One way this drug may act is increasing glutamate and GABA transporters in astrocytes (Ueda et al., 2007). Chronic administration of levetiracetam may attenuate glutamate excitotoxicity and increase inhibitory neurotransmission. This molecular mechanism involving astrocytes may result in a reduction of cognitive abnormalities in AD.

A β Clearance

Astrocytes also participate in the degradation and removal of A β as they express different types of proteases involved in the enzymatic cleaving of A β . The metalloendopeptidases NEP, IDE, and ECE1 and ECE2 have been reported to be expressed in astrocytes, and are involved in the degradation of monomeric A β species (although NEP also hydrolyze oligomeric

forms) (Mulder et al., 2012; Ries and Sastre, 2016). It has been proposed that the modification from “natively folded-active” to “aggregated-inactive” form of IDE and NEP may be a relevant pathological mechanism in late-onset AD (Dorfman et al., 2010). Astrocytes also express and secrete several MMPs, including MMP-2 and MMP-9, which degrade both monomeric and fibrillar extracellular forms of A β (Ries and Sastre, 2016). Furthermore, it was found in APP/presenilin 1 transgenic mice that astrocytes surrounding A β plaques increased the expression of both MMP-2 and MMP-9 (Yan et al., 2006; Yin et al., 2006).

Apolipoprotein E is primarily produced by astrocytes in the CNS and has been proposed to play a major role in AD. In mice, ApoE(–/–) astrocytes have been shown to fail to respond or internalize A β deposits to the same extent as do wild-type astrocytes (Koistinaho et al., 2004). As well, mice astrocytes expressing the ApoE ϵ 4 allele were less effective eliminating A β plaques than those astrocytes expressing the ApoE ϵ 3 allele (Simonovitch et al., 2016). Astrocytes derived from human induced pluripotent stem cells (iPSC) which expressed the ApoE ϵ 4 allele failed to support neuronal neurotrophic functions such as survival and synaptogenesis (Zhao et al., 2017). As the presence of ApoE ϵ 4 allele is considered a major risk factor in AD while the presence of ApoE ϵ 2 allele is considered a protective factor, a differential regulation of these isoforms regarding the presence of A β and associated responses such as neuroinflammation has been proposed (Dorey et al., 2017).

AD and Astrocyte Imaging

One of the most important research areas in AD is related to the development of biomarkers. Although several types of biomarkers have been explored, there is still not one that specifically diagnose, differentiate, and predict the rate of decline between populations of cognitively healthy/preclinical dementia, mild cognitive impaired and AD individuals (Fiandaca et al., 2014; Salvatore et al., 2015; Huynh and Mohan, 2017). Due to their fundamental role in CNS homeostasis, astrocytes could be considered as possible targets for tracking and studying *in vivo* changes in AD as well as serving as a biomarker for the disease.

L-Deprenyl is a selective inhibitor of the enzyme MAO-B, predominantly found on astrocytes (Levitt et al., 1982). This compound has been successfully used *in vitro* and *in vivo* to study the distribution and activity of MAO-B through different techniques including quantitative autoradiography and positron emission tomography (PET) (Kumlien et al., 1992; Arakawa et al., 2017). In postmortem samples from individuals with AD, the activity of both MAO-B and the binding of [3H]L-deprenyl was found to be increased in many brain regions (Jossan et al., 1991). In addition, MAO-B has been found to be increased during reactive astrocytosis in neurodegenerative conditions (Ekblom et al., 1993, 1994). As astrocytes produce MAO-B and this enzyme is increased during reactive astrocytosis, which is a process observed in AD, it seemed plausible to use L-deprenyl as a marker of astrocytosis in this condition.

Accruing evidence seems to support the use of L-deprenyl in AD. A comparative study using PET between one of the currently accepted biomarkers for AD, the 11C-Pittsburgh Compound B, and (11)C-deuterium-L-deprenyl, concluded that the latter

provided non-redundant information on both functional and pathologic aspects of the disease (Rodríguez-Vieitez et al., 2016a). Furthermore, L-deprenyl has provided valuable information about the stage of progression of AD. In a human study, the highest binding for (11)C-deuterium-L-deprenyl was observed in Braak I–II (initial AD stages), whereas it decreased with the most advanced Braak stages (Gulyás et al., 2011). Similar results have been obtained in other studies using (11)C-deuterium-L-deprenyl, where astrogliosis is prominent at the initial phases, even at preclinical stages, and then declines as the disease progresses (Carter et al., 2012; Schöll et al., 2015; Rodríguez-Vieitez et al., 2016b). In addition, a similar laminar binding pattern for tau and [3H]L-deprenyl at the temporal lobe was recently demonstrated, suggesting tau deposits and astrocytic inflammatory processes are closely related in AD (Lemoine et al., 2017). All these results point to an early contribution of astrocytes in AD pathology.

GABA–Glutamine Cycle

Neurons and astrocytes work in a coordinated way throughout different metabolic pathways to synthesize and release glutamate and GABA (Bak et al., 2006). At inhibitory synapses this pathway is called the GABA–glutamine cycle and it depends on GABA transporters and a multi-enzyme machinery that coordinates this process (i.e., GABA transaminase, glutamate decarboxylase, and glutamine synthetase) (Bak et al., 2006; Hertz, 2013). In AD, the processes related to GABA–glutamine cycle and GABA release from astrocytes seem to be altered. The glutamine–glutamate/GABA cycle consists of the transfer of glutamine from astrocytes to glutamatergic and GABAergic neurons. This process depends on glutamine synthetase and the tricarboxylic acid cycle (Walls et al., 2015). A reduction in pyruvate carboxylation, glutamine levels, and tricarboxylic acid cycle turnover in GABAergic neurons and astrocytes was shown in the transgenic rat AD model, McGill-R-Thy1-APP (Nilsen et al., 2014). Similarly, reduced expression of glutamine synthetase in postmortem AD brain samples indicates a profound alteration in neurotransmitter and protein synthesis, as well as metabolic dysfunction (Robinson, 2000). Astrocytes may produce and release GABA, with a main role on hippocampal synaptic plasticity function during memory processing. Increased activity of glutamate decarboxylase enzyme was found in glial synaptosomes obtained from the cortex of APP/TS1 transgenic mice, suggesting A β plaques stimulate GABA synthesis from astrocytes (Mitew et al., 2013). Reactive astrocytes from APP/PS1 transgenic mice have also been shown to produce GABA involving MAO-B, and release it through the bestrophin 1 channel, in an aberrant manner (Jo et al., 2014). In the same study, the suppression of GABA production or release from astrocytes completely restored the cognitive deficits and impairments in synaptic plasticity observed in the mice. Under physiological conditions, astrocytic GABA exerts a disinhibitory action at the perforant path to dentate gyrus neurons via GABA $_B$ receptors on interneurons. However, in the APP^{swe}/PSEN1^{dE9} mice, it has been shown an inhibitory action of astrocytic GABA by targeting GABA $_A$ receptors in glutamatergic terminals (Yarishkin et al., 2015). These results

provide a useful specific GABAergic target aimed at memory impairment reduction in AD. Alterations in the metabolic functions of astrocytes and consequently in glutamate and GABA–glutamine cycles may help explain cognitive disorders in AD (Le Prince et al., 1995; Robinson, 2000; Nilsen et al., 2014). Neurotransmitter transporters and effectors together with GABA-metabolizing enzymes are of special interest in drug development regarding therapeutical options for GABA-related neurological dysfunctions such as AD (Sarup et al., 2003; Nava-Mesa et al., 2014; Mutis et al., 2017; Sánchez-Rodríguez et al., 2017). Although special attention should be taken regarding the differential functional roles of neuronal and glial neurotransmitter transporters and overlying GABA/glutamate metabolic pathways in the development of high selective cell-specific drugs, in order to avert pharmacological interactions and unexpected side effects.

Metabolic Compromise

The metabolic cooperation between astrocytes and neurons is essential to the brain functioning. The energy metabolism of neurons depends on blood oxygen supply but also on astrocytic glucose transporters, mainly GLUT1 (Morgello et al., 1995). In addition, astrocytes may convert glycogen to lactate during periods of higher activity of the nervous system (Falkowska et al., 2015). Both *in vivo* and *in vitro* studies indicate that astrocytes participate in the regulation of cerebral blood flow according to neuronal activity and metabolic demand (Magistretti and Pellerin, 1999; Magistretti, 2006). Therefore, astrocytes are key to guarantee an adequate coupling between brain activity and metabolic supply. Several studies have shown reduced cerebral glucose metabolism in early stages of AD and correlation with symptoms severity (Desgranges et al., 1998; Mosconi et al., 2005, 2006, 2008). As mentioned early, A β affects neuronal excitability and it also may reduce astrocytic glycolytic capacity (Soucek et al., 2003; Schubert et al., 2009) and reduce the neurovascular unit function (Acosta et al., 2017; Kisler et al., 2017). Moreover, reductions in GLUT1 and lactate transporters in astrocyte cultures derived from transgenic AD mice have been reported (Merlini et al., 2011). In AD, the resulting metabolic dysfunction may alter the overall oxidative neuronal microenvironment (Mosconi et al., 2008). The chronic sustained effect of diminished lactate supply, increased neuronal activity, and reduced neurovascular coupling, underlines the OS increase during AD. Therefore, astrocytes are crucial players either acting as protectors against OS or participating in the progression of AD. The specific role of astrocytes on inflammatory response and OS damage will be reviewed in the next sections.

NEUROINFLAMMATION, ALZHEIMER'S DISEASE, AND ASTROCYTES

Inflammation is a protective physiological response necessary to regulate processes associated with damage mechanisms in the organism. Several actions related to general inflammatory activities include protection against microorganisms, tissue repair, and removal of cellular debris. The CNS possesses some

characteristics that differentiate the immune and inflammatory activities of the brain and spinal cord from those occurring in the rest of the body. Mainly, these differences arise through the presence of the BBB, which restricts the pass of leukocytes into the brain parenchyma, and also due to the cellular interactions of microglia and astrocytes, responsible for most of the immune/inflammatory CNS responses (Ransohoff et al., 2015). Although neuroinflammation arises innately as a protective mechanism when injury is present in the CNS, alteration in any of the components of this response may compromise the cellular microenvironment and become noxious to the brain. Many neurodegenerative conditions, including AD, have been associated with the presence of abnormal neuroinflammation (Ransohoff, 2016).

The role of astrocytes in neuroinflammation has been highlighted in the past years with many observations both *in vivo* and *in vitro* depicting the importance of these glial cells in this process (Colombo and Farina, 2016). In fact, an increase in the expression of GFAP is commonly considered as a hallmark of neuroinflammation in many neurodegenerative conditions, including AD (Millington et al., 2014). Astrocytes, together with microglia, react to a diverse range of pro- and anti-inflammatory agents (Sofroniew, 2014). Depending on the cytokine, astrocytes modify their phenotype to either activated or deactivated state. Increased levels of INF- γ , IL-1 β , IL-6, and TNF α induce astrocytes to adopt a classical activation state (increased activation of NF- κ B pathway, production of ROS and NO, and release of IL-1 β , IL-6, and TNF α), while increased levels of IL-4 and IL-13 induce an alternative activation (increased secretion of IL-4 and decreased production of ROS and NO); oppositely, high levels of IL-10 and TGF- β induce astrocytic deactivation (reduced immune surveillance and proinflammatory signaling) (Dá Mesquita et al., 2016).

Furthermore, the reactive state of astrocytes may also depend on the source of injury (neuroinflammation or ischemia), indicating the complex range of responses these cells are capable to produce (Zamanian et al., 2012). In a recent paper, a new classification of reactive astrocytes was proposed, designating A1 those astrocytes that developed a neurotoxic phenotype and A2 those that depicted neurotrophic and neuroprotective characteristics (Liddelow et al., 2017). The authors also reported that the presence of IL-1 α , TNF α , and C1q (all three released from microglia) promoted the appearance of A1 astrocytes and that this phenotype was found to be predominant in brain tissue from AD patients. These findings raise a number of questions regarding the manner in which the brain deals with different types of injuries and specifically how astrocytes and astrocytic-cellular interactions induce either a protective or harmful profile. An increase in A1 astrocytes seems to occur in AD, but still is not clear if A β induces this phenotype or if another specific agent is involved in this reaction. Nonetheless, it has been reported that the interaction of A β with astrocytes induces a pro-inflammatory profile and even astrogliosis (Batarseh et al., 2016).

RAGE, Astrocytes, and Amyloid Beta

Amyloid beta has been reported to interact with numerous cellular receptors and astrocytes express a large amount

of them, including TLRs, scavenger receptors, glycoprotein receptors, lipoprotein receptors, RAGE, acetylcholine receptors, complement and chemokine receptors, T-cell receptors, and mannose receptor, among others (Farfara et al., 2008). Binding of A β to different types of receptors seems to depend on the A β peptide form (monomer or fibrillar). For example, IR- and SEC-R bind monomeric forms of A β , scavenger receptor CD36 and glycoprotein receptors lactadherin, and CD47 prefers fibrillary A β , while RAGE, ApoE, and nAChR α 7nAChR bind both monomer and fibrillar forms (Verdier et al., 2004). The specific outcome of all these complex A β -astrocytic interactions is still under research, as the precise intracellular and intercellular communication changes prompted by the different types of A β acting on these receptors is yet to be elucidated. Despite the gaps in knowledge, the activation of some receptors, in particular RAGE, has been reported to induce proinflammatory changes in astrocytes when exposed to A β (González-Reyes and Graciela Rubiano, 2016).

Advanced glycation end products receptor is a multiligand pattern-recognition receptor, member of the immunoglobulin superfamily with a variety of isoforms present in brain cells (Ding and Keller, 2005). In addition to A β and several AGE, RAGE can bind DNA-binding protein HMGB1/amphoterin (Hori et al., 1995) and S100/calgranulins (Hofmann et al., 1999). The main intracellular pathway activated through RAGE is the NF- κ B pathway (Tóbon-Velasco et al., 2014), although it can also activate other downstream pathways including Cdc42-Rac, p21ras and MAPK, JNK, and ERK (González-Reyes and Graciela Rubiano, 2016). Furthermore, astrocytes have been reported to adopt a phagocytic profile capable of engulfing A β , mediated by CD36, CD47, and RAGE receptors (Jones et al., 2013). Apart from A β , the interaction of astrocytic RAGE with other ligands, such as S100B, may also be involved in AD neuroinflammation (Cirillo et al., 2015). These findings point to the interaction of RAGE/NF- κ B pathway in astrocytes as an important factor in the development or maintenance of inflammation in AD.

Astrocytes and NF- κ B Pathway

The transcription factor NF- κ B is currently considered as an important agent related to neuroinflammation in AD (Shi et al., 2016). NF- κ B is known to be mainly activated by two pathways, the canonical (or classical) and the non-canonical (or alternative) (Nakajima and Kitamura, 2013). The canonical pathway involves activation of various receptors including RAGE and cytokine receptors, such as TNF receptor, IL-1 receptor, and the TLR family. These will induce the further activation of many downstream agents, in special IKKs alpha (IKK α) and beta (IKK β), and NEMO (in charge of the degradation of the cytoplasmic inhibitor IKB α), and the subsequent complexes (mainly RelA) that act as transcription factors in the nucleus (Marcu et al., 2010; Wan and Lenardo, 2010). The non-canonical pathway, also known as the NEMO-NF- κ B-independent pathway, occurs when NF- κ B is activated by specific recruitment of TRAF2 and TRAF3, and involves p52 and RelB (Morgan and Liu, 2011). Both canonical (Wang et al., 2013) and non-canonical (Akama and Van Eldik, 2000) activation of NF- κ B has been observed in astrocytes stimulated

with A β , but still is not clear which type predominates in AD or if a differential NF- κ B activation is related to the stage of the disease. It has been reported that most of the cytokines and chemokines produced by non-stimulated and activated astrocytes are direct targets of the NF- κ B pathway, suggesting a central role of this factor in the proinflammatory (neurotoxic) and immunoregulatory (neuroprotective) actions of astrocytes in the CNS (Choi et al., 2014). Also, NF- κ B is involved in other functions such as neuronal survival, differentiation, apoptosis, neurite outgrowth, and synaptic plasticity, all found to be altered in AD (Mémét, 2006).

In astrocytes and microglia, the activation of NF- κ B due to A β stimulation leads to the production of the pro-inflammatory cytokines IL-1 β , IL-6, iNOS, and TNF α (Bales et al., 1998; Akama and Van Eldik, 2000; Hou et al., 2011). In rats treated with A β _{1–42} oligomers, it was shown that COX-2, IL-1 β , and TNF α were expressed in reactive astrocytes surrounding the A β -injection site and in nearby blood vessels, as well as found co-localization of NF- κ B proteins with GFAP and COX-2 (Carrero et al., 2012). In primary astrocytic and mixed astrocytic-neuronal cell cultures from rats, the use of minocycline, an anti-inflammatory agent, reduced astrocytic inflammatory responses together with a decrease in neuronal loss, caspase-3 activation, and caspase-3-truncated Tau species in neurons (Garwood et al., 2011). Minocycline has been shown to inhibit the NF- κ B signaling pathway in spinal rat astrocytes (Song et al., 2016). Other reports of beneficial outcomes due to regulation of the NF- κ B signaling pathway in astrocytes were reviewed by Colombo and Farina (2016). Although an exaggerated neuroinflammatory response is observed in AD, an absolute suppression of the NF- κ B signaling pathway may be undesirable and even worsen the pathological condition. In APP^{swe}/PS1^{dE9} transgenic mice, the suppression of NF- κ B attenuated astrogliosis in the hippocampus and cortex of the animals but increased the amount of A β _{1–42}, suggesting a role of astrocytic-mediated neuroinflammation in the clearance of A β (Zhang et al., 2009). As well, the clinical evidence for the use of non-steroidal anti-inflammatory drugs (NSAIDs) in AD patients has not proven to be of benefit (Aisen et al., 2008; Szekely et al., 2008; Beeri et al., 2012; Alzheimer's Disease Anti-inflammatory Prevention Trial Research Group, 2013).

Inflammatory Induction of A β in Astrocytes

Astrocytes not only are activated and induced to release chemokines and cytokines in the presence of A β , these cells also react to the presence of pro-inflammatory cytokines and even increase the production of A β in response. Therefore, the presence of inflammation is capable of increasing the production of A β . In addition, the development of neuroinflammation has also been related to cognitive changes in AD (Westin et al., 2012; Echeverria et al., 2016; Laurent et al., 2017).

Neuroinflammation in AD is characterized by the accumulation of cytokines such as IL-1 β , IL-6, TNF- α , or TGF- β , which can contribute with cerebral amyloid deposition, augmentation of APP expression, A β formation, and subsequent recruitment and activation of microglial cells (Esler and Wolfe,

2001). In general, TNF- α , IL-1 β , IFN- γ , L-6, and TGF- β are able to stimulate β -secretase and γ -secretase enzymatic activity through a JNK-dependent MAPK pathway, which cleaves APP and initiates A β formation (Liao et al., 2004). Astrocytes express and respond to a large scope of cytokines and chemokines suggesting a central role in the inflammatory-induced production of A β .

A study reported that a systemic immune challenge in wild-type mice during late gestation induced the development of AD-like pathology during aging, with animals displaying increased levels of hippocampal APP and altered Tau phosphorylation, together with microglia and astrocytic activation (Krstic et al., 2012). Additionally, it was shown that LPS-induced systemic inflammation in mice could contribute to cognitive impairment and increased expression of APP and A β _{1–42}, associated with increased production of inflammatory mediators such as COX-2, IL-1, and iNOS (Lee et al., 2008). The same paper reported that these changes were accompanied with astrocytic activation. Other studies have found evidence, both in human and murine models, that inflammation induces the expression of A β . Primary astrocytes from mice, treated with a combination of TNF α and INF- γ , significantly increased levels of BACE1, APP, and A β _{1–40} (Zhao et al., 2011). In human primary astrocytes, treatment with INF- γ in combination with either TNF α or IL-1 β induced the secretion of A β _{1–40} and A β _{1–42} (Blasko et al., 2000). Furthermore, TGF- β 1 was found to induce overexpression of APP in astrocytes but not in neurons (Lesné et al., 2003). Cytokines seem to act on the 5'-untranslated region (5'-UTR) of the APP gene in astrocytes (Lahiri et al., 2003).

On the one hand, it seems that the presence of A β is able to induce the production and release of pro-inflammatory cytokines and chemokines from astrocytes, which could as well act in an autocrine manner to further induce the production of A β from astrocytes and possibly other cells. On the other hand, these results suggest that inflammation may be present at early stages (pre-clinical) of the disease or even that inflammation may be responsible for the appearance of pathological A β production and accumulation. Under both circumstances, astrocytes appear to be deeply involved in inflammatory changes observed in AD.

Astrocytes and Other Mechanisms of Neuroinflammation

Other factors related to astrocytes may contribute to the appearance or enhancement of neuroinflammation in AD. For example, the presence of elevated glucose levels (as found in diabetes) has been shown to increase neurotoxicity and the release of pro-inflammatory cytokines from primary human astrocytes (Bahniwal et al., 2017). A relation between AD and diabetes/metabolic syndrome has been explored previously (González-Reyes et al., 2016), as both A β and AGE bind to RAGE in astrocytes. As well, pro-inflammatory signaling in astrocytes may involve changes in the expression of the calcium-dependent phosphatase CaN, which has been shown to interact with another transcription factor involved in inflammatory responses, the NFAT (Acosta et al., 2017). Enhanced nuclear accumulation of CaN/NFAT was observed in human AD hippocampus and

astrocytic cultures treated with A β (Abdul et al., 2009). In addition, it has been reported that A β deregulates calcium homeostasis via CaN and its downstream target NF- κ B, as well as increasing NF- κ B-dependent expression of mGluR5 and IP3R2 in astrocytes (Lim et al., 2013). Changes in mGluR5 and IP3 receptor expression have been reported in astrocytes surrounding amyloid plaques in a genetic mouse model of AD (Norris et al., 2005). Another possible factor contributing to the presence of neuroinflammation is the BBB, as in AD, it has been reported that the BBB occasionally loses its integrity (Chakraborty et al., 2017). This may be explained in part thanks to the accumulation of A β in brain blood vessels and also due to the associated vascular inflammation, allowing crossed communication between the peripheral immune system and the brain (Takeda et al., 2014). As astrocytes have a very important interaction with the BBB and its functional components are plausible to consider their involvement in BBB-associated neuroinflammatory changes in AD.

Uncontrolled neuroinflammation is a critical element in the progression of AD, impairing the normal function of the CNS. Astrocytes, together with microglia, are the main cells involved in the inflammation/immune responses of the CNS. The presence of A β activates different astrocytic cell receptors, mainly RAGE, inducing the activation of the inflammatory pathway NF- κ B responsible for the transcription of numerous pro-inflammatory cytokines and chemokines in astrocytes. In addition, the presence

of pro-inflammatory cytokines such as IL-1 β can act on astrocytes stimulating the production of A β and perpetuating a pro-inflammatory profile in astrocytes. Astrocytes are key in the maintenance of the homeostatic balance of the CNS and use the mechanism of reactive astrogliosis as a defensive reaction (Pekny et al., 2016), therefore is fundamental to understand the pathophysiological process that causes astrocytes to convert from a protective agent into a cell that produces a maladaptive astrogliosis response in AD (Table 1).

OXIDATIVE STRESS, ALZHEIMER'S DISEASE, AND ASTROCYTES

Oxidative stress is the result of a dysregulation between the amount of free and non-free radicals produced, including ROS and RNS. This can be attributed to the loss of homeostasis due to mitochondrial overproduction of oxidants over the production of antioxidants (Swomley and Butterfield, 2015). Among the most important ROS are the peroxy radicals (ROO \cdot), NO, the superoxide radical anion (O $_2^{\cdot-}$), the hydroxyl radical OH \cdot and some other non-radical species such as peroxynitrite (ONOO $^-$), single oxygen (O $_2$), and hydrogen peroxide (H $_2$ O $_2$) (Dasuri et al., 2013). ROS, as well as RNS, are produced under physiological conditions during the common metabolic pathways. These reactive species act on second messengers

TABLE 1 | Summary of studies reporting effects of A β or AD on pro-inflammatory and anti-inflammatory cytokines and chemokines in astrocytes.

| Experimental model | Pro-inflammatory agents | Anti-inflammatory agents | Reference |
|--|--|---|---|
| Primary culture of rat astrocytes treated with A β_{1-42} | \uparrow TNF α ; \uparrow IL-1 β ; \uparrow IL-6; \uparrow COX-2; \uparrow PGE2; \uparrow IL-17; \uparrow INF- γ ; \uparrow IP-10 | \uparrow IL-13 | Hu et al., 1998; Akama and Van Eldik, 2000; Garwood et al., 2011; Wang et al., 2013; Aguirre-Rueda et al., 2015 |
| Isolated rat astrocytes treated with A β_{25-35} | \uparrow TNF α ; \uparrow IL-1 β | | Del Bo et al., 1995; Ayasolla et al., 2004 |
| Primary cultures of rat astrocytes treated with A β_{1-40} | \uparrow IL-1 β ; \uparrow IL-6 | | Bales et al., 1998 |
| Mixed cultures of rat neurons and astrocytes treated with A β_{1-42} and A β_{25-35} | \uparrow TNF α | | Masilamoni et al., 2005b |
| Primary cultures of rat astrocytes treated with spherical aggregates of synthetic A β | \uparrow IL-1 β | | Todd and Garrard, 1979 |
| <i>In vivo</i> i.c. infusion of A β_{1-42} oligomers in rats | \uparrow IL-1 β ; \uparrow TNF α ; \uparrow COX-2 | | Carrero et al., 2012 |
| Primary culture of mice astrocytes treated with A β_{1-42} | \uparrow IL-1 β ; \uparrow IL-6; \uparrow TNF α | \downarrow TGF- β 1 | Liu et al., 2009; Hou et al., 2011 |
| Brain sections of Tg2576 mice stained for GFAP | \uparrow IL-1 β ; \uparrow IL-6; \uparrow INF- γ ; \uparrow IL-12 | \uparrow TGF- β 1; \uparrow IL-10 | Mehlhorn et al., 2000; Apelt and Schliebs, 2001; Abbas et al., 2002 |
| <i>In vivo</i> i.c.v infusion of A β_{1-42} oligomers in mice | | \downarrow TGF- β 1 | Diniz et al., 2017 |
| <i>In vivo</i> i.c.v infusion of A β_{1-42} in IL-32 β transgenic mice | \uparrow IP-10; \uparrow GM-CSF | \uparrow IL-13 | Yun et al., 2015 |
| Astrocytoma human cell line U-373 MG treated with A β_{1-40} (co-treated with IL-1 β) | \uparrow IL-6 | | Gitter et al., 1995 |
| Postmortem brain tissue from patients with AD, stained for GFAP (or other astrocytic marker) | \uparrow IL-1 β ; \uparrow IL-6; \uparrow IL-18 | | Ojala et al., 2009; Bouvier et al., 2016 |

TNF α , tumor necrosis factor alpha; TGF- β 1, transforming growth factor beta 1; COX-2, cyclooxygenase-2; PGE2, prostaglandin E2; GFAP, glial fibrillary acidic protein; IP-10, interferon gamma-induced protein 10; GM-CSF, granulocyte-macrophage colony-stimulating factor; i.c., intracerebral; i.c.v., intracerebroventricular.

and subsequently may influence several signaling pathways in a positive or negative form, depending on the regulatory mechanism of its concentration, called redox regulation (Valko et al., 2007). Likewise, mitochondria are able to produce antioxidants which counteract the harmful effects of OS to maintain the balance between the production and detoxification of ROS. These antioxidants are classified in two main groups: enzymatic antioxidants such as SOD, catalase, antioxidant GSH, GPX, GSH reductase, and GSH-S-transferase, and non-enzymatic antioxidants such as GSH, thioredoxin, vitamins A, E, and C, flavonoids, and proteins like albumin and metallothionein (Valko et al., 2007; Halliwell, 2012).

Oxidative Stress and Alzheimer's Disease

The development of OS in AD has been related to mitochondrial dysfunction, leading to superoxide overproduction ending in synaptic damage (Friedland-Leuner et al., 2014; Bhat et al., 2015). Mitochondrial dysfunction in AD seems to be linked to the increased presence of ROS and RNS (Islam, 2017). Müller et al. (2010) observed a decreased mitochondrial potential in transgenic Thy1-APP751SL mice. The same authors reported that increased intracellular A β production might trigger mitochondrial dysfunction quite early and independently of A β plaques and, that the accumulation of these alterations with aging lead to disruption of respiratory chain complexes (mainly III and IV) and significant reduction in the generation of NADH. The authors suggested that progressive increase in oxidant production together with a decrease in antioxidant components may conduce to the loss of brain homeostasis observed in AD. However, in AD, it has been demonstrated that prior to the appearance of senile plaques, brains present glucose hypometabolism due to abnormal oxidative metabolic routes in the mitochondria, which also induce increased ROS production and subsequent oxidative cell damage (Maruszak and Żekanowski, 2011). Additionally, variants of gene expression profiles in AD have shown downregulated expression of NeuroD6, which encodes a transcription factor involved in triggering antioxidant responses and the maintenance of the production of mitochondrial antioxidants (Uittenbogaard et al., 2010; Fowler et al., 2015). Also, RNA-Seq and microarray data analysis indicated a consistent downregulation of NeuroD6 in brains of individuals with AD, suggesting downregulation of NeuroD6 as a possible biomarker for AD (Satoh et al., 2014).

The role of ROS and OS in neurodegenerative diseases, including AD, is not entirely clear, although it has been observed that a modest level of oxidative RNA damage occurs during the process of aging in brain neurons, but a prominent level of oxidative RNA damage is present in vulnerable neurons which correspond to the earliest stage of cognitive decline in the transition from cognitively normal aging to AD (Nunomura et al., 2012). Furthermore, DNA bases are vulnerable to OS damage involving hydroxylation, protein carbonylation, and nitration in AD (García-Blanco et al., 2017). Changes in oxidative markers have been reported in brain regions such as hippocampus and

inferior parietal cortex, which are also compromised in AD (Floyd and Hensley, 2002).

Brain is considered to be especially vulnerable to OS and susceptible to lipid peroxidation because of its high lipid and poly-unsaturated fatty acids content, and its low concentrations of antioxidants (Butterfield et al., 2013). In AD, neurotoxic effects of A β induce OS through lipid peroxidation, protein degradation, and amino acid oxidation, which in turn increase the production of ROS and RNS by positive feedback (Swomley and Butterfield, 2015). Alkenals, 4-hydroxynonenal (HNE), and 2-propenal (acrolein) are reactive products obtained from lipid peroxidation induced by A β . These agents can modify covalently some amino acids residues or change protein conformation, which in turn affects its function. Thus, a coupling between increased lipid peroxidation and structural modification of GLT-1 has been proposed, explained by increased HNE binding due to excessive A β_{1-42} (Butterfield et al., 2002). These events can compromise astrocyte function, inducing glutamate transport inhibition and increasing excitotoxicity to neurons in AD.

Astroglia Role in Oxidative Stress

Astrocytes seem to be involved in the processes leading to the appearance or maintenance of OS in AD. Abramov et al. (2004a), working in rat astrocytes, have shown that A β treatment increases intracellular-free calcium influx from the extracellular space, and induces changes in mitochondrial functions. These changes are associated with the activation of NOX due to A β interaction on the membrane, which, in turn, induces [Ca²⁺]_i changes. The main changes leading to mitochondrial dysfunction in astrocytes are associated with mitochondrial depolarization, increased conductance, and presence of mitochondrial permeability transition pores (Duchen, 2000). A possible mechanism which explains why calcium influx is induced by A β into astrocytes could be related with the formation of calcium selective channels on the membrane, which seem capable of generating a different conductance (Abramov et al., 2004b). These channels have been shown to be formed by insertion of A β peptides in the membrane, and also are arranged in a structural configuration which requires a lesser content of cholesterol on the lipidic membrane (Kawahara and Kuroda, 2001; Arispe and Doh, 2002; Arispe et al., 2007).

Additionally, it has been found that A β_{1-42} oligomers are key factors on the induction of OS stress by astrocytes. A β_{1-42} oligomers binding to RAGE on astrocytes induce ROS production via NOX complex activation (Askarova et al., 2011). However, astrocytes are also able to trigger ERK1/2 pathways and cytosolic phospholipase A2 phosphorylation, independent of NOX activation, which in turn causes mitochondrial dysfunction by decreasing mitochondrial membrane potential, enhancement of NOX activity, and overproduction of ROS (Zhu et al., 2006). Astrocytes seem to be a primary target of A β , as this peptide induces various effects related to OS such as altered intracellular calcium signaling and calcium-dependent reduction in astrocytic GSH (Abramov et al., 2004b). Although this GSH depletion affects astrocytes, neurons are the cells that show a higher rate of cell death, suggesting that neurotoxicity reflects the neuronal dependence on astrocytes for antioxidant support.

This could better be explained by the fact that astrocytes are the producers of the primary elements required for the production of GSH in neurons, such as glycine and cysteine (Abramov et al., 2003; Gandhi and Abramov, 2012). Regarding GSH, it has also been shown that in cultured astrocytes, a prolonged incubation with A β reduces induction of the transporter ABCC1 which is the main pathway for GSH release (Ye et al., 2015). Astrocytes play a central role in maintaining the neuronal integrity, nevertheless cytokines and neurotransmitters released by damaged or activated astrocytes may increase the neurotoxicity and vulnerability of neurons. During chronic OS, as observed in AD, the crosstalk communication between astrocytes and neurons is impaired resulting in disrupted memory consolidation. This compromise in memory formation is probably due to calcium overload and activation of MAPK pathways in astrocytes, which involve as well the JNK/SAPK pathways, and may conduce to anomalous deleterious signaling, including autophagic astroglial signals and apoptosis (Ishii et al., 2017).

Oxidative Stress and the Connection with Neuroinflammation

During neuroinflammation, increased concentrations of ROS/RNS may lead to the activation of the transcription factor NF- κ B which induces the overexpression of NO synthases in astrocytes and microglia, in particular NOX2 and iNOS, resulting in peroxynitrite production by superoxide and NO reaction producing neuronal damage (Saha and Pahan, 2006; Brown, 2007; Morgan and Liu, 2011). Moreover, NF- κ B activation induces the expression of COX-2 and cytosolic phospholipase A2, which in turn stimulate the generation of prostaglandins, promoting inflammation and OS (Hsieh and Yang, 2013). Castegna et al. (2003) reported that the formation of peroxynitrite ONOO⁻ leads to protein nitration in enzymes, such as alpha and gamma enolases, implicated in brain glucose metabolism. Thus, the signaling pathway NF- κ B, which is also heavily involved in inflammatory reactions, has been proposed to be involved in OS, as a direct crosstalk between ROS and NF- κ B has been reported (Turillazzi et al., 2016). In AD, the presence of chronic OS alters the protective physiological role of the NF- κ B transcription pathway, which normally promotes cell survival and prevents apoptosis and necrosis, through modulation of the JNK signaling pathway (Morgan and Liu, 2011). In astrocytes, it was reported that under certain conditions, IL-1 β may act stimulating astrocytic GSH production, and potentially, augmenting total antioxidant capacity in the brain, via an NF- κ B-dependent process (He et al., 2015). In this way, NF- κ B pathway has been associated with both pro-oxidant and antioxidant roles. In AD, an alteration of this pro- and anti-oxidant role of NF- κ B in astrocytes seems to be present, tending toward a pervasive pro-oxidative and pro-inflammatory profile (Table 2).

Novel anti-Alzheimer's drugs will need to consider the selective modulation of astrocyte activity in order to reduce pro-inflammatory signaling as well as to attenuate OS and diminish excitotoxicity (Figure 1). Taking into account the complex pathophysiology of AD, a deep knowledge about

dysfunctional astrocyte intracellular pathways evoked by A β opens the possibility for the design of new effective multi-target directed drugs.

NOVEL NEUROPROTECTIVE AND THERAPEUTIC MEASURES IN ALZHEIMER'S DISEASE

Alzheimer's disease is a major neurodegenerative disease affecting millions worldwide without a known curative treatment. Currently, only five drugs have been approved by the Food and Drug Administration (FDA) of the United States, three cholinesterase inhibitors (donepezil, galantamine, and rivastigmine), an NMDA receptor antagonist (memantine) and a combined donepezil-memantine drug. The cholinesterase inhibitors are approved for symptomatic treatment of mild-to-moderate stages of AD, while the NMDA antagonist is used for moderate-to-late stages. Regrettably none of these drugs is able to halt the progression of the disease and its uses are aimed at maximizing the quality of life of patients through broad symptom management (Caselli et al., 2017). It is therefore of great importance to design and develop new treatments which offer better therapeutic outcomes and disease-modifying responses to the patients with AD. Epidemiologic studies indicated that prolonged treatment with anti-inflammatory agents such as non-steroidal anti-inflammatory drugs could delay AD onset, as well as reduce disease rate progression (McGeer et al., 1990; Pasinetti, 2002; Cudaback et al., 2014). The inhibition of COX-mediated signaling pathways may reduce some inflammatory cytokines related with the pathophysiology of AD. In addition, human studies confirm that OS plays a main role in the pathophysiology of AD (Schrage et al., 2013; Chang et al., 2014). However, there are some controversies between observational studies and randomized controlled trials about the efficiency of antioxidative agents and anti-inflammatory drugs to reduce AD risk (Viña et al., 2004; Cudaback et al., 2014; Wang et al., 2015; Jiang et al., 2016). Many research groups and pharmaceutical companies have been developing new strategies to overcome the disease, but so far none of the A β -targeted phase three clinical trials reported has shown statistically significant benefit on its pre-specified clinical endpoints (Selkoe and Hardy, 2016). Many explanations may be offered for this lack of success, ranging from poorly designed trials to late interventions (irreversible modification of the disease due to advanced stage) but also, to the incomplete knowledge about the basic pathophysiological mechanisms of AD. As astrocytes have been shown to be involved in a diverse range of pathological changes observed in AD, they have been proposed as an interesting novel therapeutic target (Finsterwald et al., 2015). Because increased proinflammatory cytokines induced by A β are associated with enhanced production of free radicals in the astrocytes (Masilamoni et al., 2005a), new compounds with antioxidative and anti-inflammatory properties could reduce the effects of neurodegeneration in AD.

Various approaches involving astrocytes have been reported recently and some of them offer promising results in *in vitro*, animal, and preclinical models for the treatment of AD. In

TABLE 2 | Summary of studies showing astrocytic-induced OS in several models of AD.

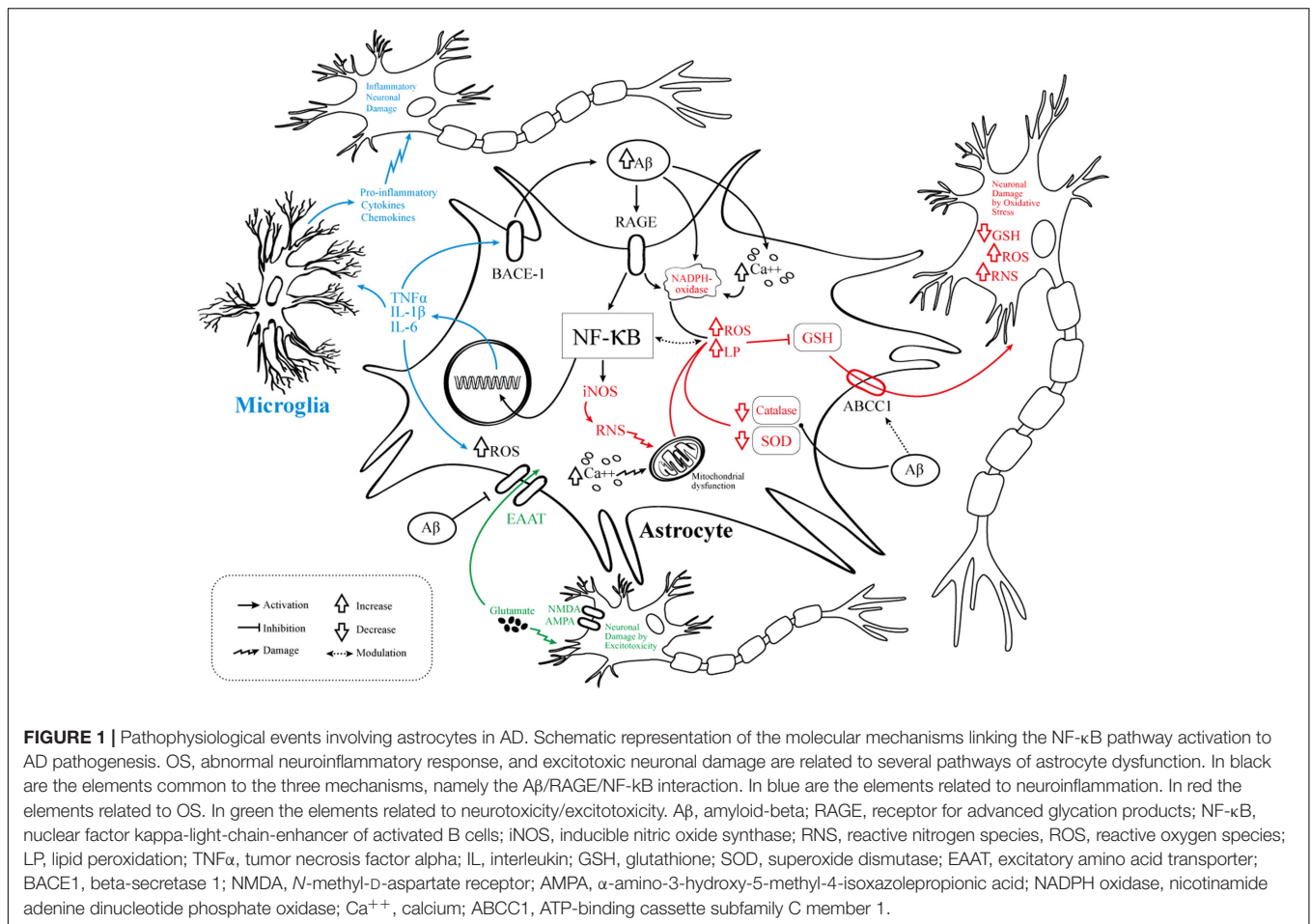
| Experimental model | Prooxidative | Antioxidative | Reference |
|---|---|--|--|
| Isolated cortical astrocytes; hippocampal neurons and astrocytes in coculture, and preparations of astrocytes from rat hippocampus (A β _{25–35} , A β _{1–42}). | ↑NOX; mitochondrial depolarization; ↑ROS | ↓GSH | Abramov et al., 2004a |
| Primary culture of cortical rat astrocytes (A β _{1–42}). | ↑NOX; ↑ROS; mitochondrial depolarization; ↑iNOS | ↓Cu/Zn SOD; =MnSOD | Hu et al., 1998; Zhu et al., 2006; Askarova et al., 2011; Bungart et al., 2014; Aguirre-Rueda et al., 2015 |
| Mixed cultures of rat hippocampal neurons and astrocytes. Isolated cortical astrocytes (A β _{25–35} , A β _{1–42}). | | ↓GSH | Abramov et al., 2003 |
| Cultured cortical rat astrocytes (fibrillar, oligomeric, and scrambled A β _{1–42}). | ↑iNOS and NO-derived peroxynitrite | | Akama et al., 1998; Hu et al., 1998 |
| Postmortem brains from AD patients. APP23 transgenic mice. APP induced by electrolytic cortical lesion. | ↑eNOS and iNOS | | Lüth et al., 2001 |
| AD postmortem brains. nNOS immunocytochemistry in reactive astrocytes. | ↑nNOS | | Simic et al., 2000 |
| Primary astrocyte culture derived from C57BL/6 (A β _{1–42}) and derived from 5xFAD mice. | | Acute ↑GSH after monomeric A β . Induction of ABCC1 was reduced in 6-month old 5xFAD mice. | Ye et al., 2015 |
| Intrahippocampal injection of A β _{25–35} . GFAP measured by ELISA in rats. | =iNOS | ↓Catalase | Sohanaki et al., 2016 |
| Cultured cortical rat astrocytes (A β _{25–35}). | ↑NOX | ↓Catalase; ↓SOD, ↓GSH; ↑GST | Jeong et al., 2005 |
| Isolated rat astrocyte cultures (A β _{25–35}). | ↑iNOS; ↑ROS; ↑RNS | ↑MnSOD | Ayasolla et al., 2004 |
| Mixed cultures of mice neurons and astrocytes. Isolated mice astrocytes (A β _{25–35} ; A β _{1–42}). | ↑ROS; ↑RNS | ↓SOD; ↓GSH; ↓Catalase | Masilamoni et al., 2005b |
| AD postmortem human cerebral cortex and hippocampus. Immunocytochemistry for GFAP. | | ↑MnSOD; ↓Cu/Zn SOD | Furuta et al., 1995; Maeda et al., 1997 |

ROS, reactive oxygen species; RNS, reactive nitrogen species; iNOS, inducible nitric oxide synthase; eNOS, endothelial nitric oxide synthase; nNOS, neuronal form of nitric oxide synthase; GSH, glutathione, GST, glutathione-S-transferase; GFAP, glial fibrillary acidic protein.

primary cortical rat astrocytes, the use of a light-generating nanoparticle attenuated A β -induced OS and inflammatory responses, through a reduction in the superoxide anion production and a lowering of IL-1 β and iNOS expression (Bungart et al., 2014). Curcumin, a natural phenol obtained from plants and commonly used as a spice, has been proposed to be of benefit in AD, reducing A β formation and decreasing neurotoxicity in the brain (Lim et al., 2001; Yang et al., 2005; Cole et al., 2007). In a recent study using APP/PS1 transgenic mice and primary rat mixed neuronal/glial cultures, curcumin was reported to improve spatial memory deficits and promote cholinergic neuronal function *in vivo*, and *in vitro*, attenuated the inflammatory response of both microglia and astrocytes, acting through PPAR γ , which inhibited the NF- κ B signaling pathway in these cells (Liu et al., 2016). Activation of PPAR γ with the use of the isoflavone phytoestrogen genistein showed an increase in the release of ApoE from primary astrocytes in an *in vivo* mouse model of AD (Bonet-Costa et al., 2016). In the same paper, the authors reported that treatment with genistein improved several cognitive features (hippocampal learning, recognition memory, implicit memory, and odor discrimination) as well as a reduction in the number and area of A β plaques. Neurosteroids, such as progesterone, have been proposed to offer neuroprotection in neurodegenerative diseases including AD (Liu et al., 2013). In primary cultures of rat astrocytes,

treatment with progesterone reduced A β -induced inflammatory responses (decreasing the production of IL-1 β and TNF α), and also suppressed endoplasmic reticulum stress activation together with attenuation of PERK/eIF2 α signaling (Hong et al., 2016). In addition to polyphenols, many other natural phytochemicals have shown anti-inflammatory and immunosuppressive efficacy in AD models. For example, triptolide extract inhibit activation of microglia and astrocytes in the APP/PS1 transgenic mouse model of AD (Li et al., 2016). Punicalagin, a compound derived from pomegranate, not only may reduce neuroinflammation (lowering TNF α and IL β) but also prevents OS through the reduction of iNOS, COX-2, and the production of ROS (Kim et al., 2017).

Other compounds with anti-amyloidogenic, antioxidative, and anti-inflammatory effects may have a potential role against dementia (Libro et al., 2016). For instance, the cannabinoid agonist WIN 55,212-2 has shown anti-inflammatory actions in primary cultured astrocytes after A β _{1–42} exposure. WIN pretreatment prevented IL-1 β , TNF α , and iNOS increase induced by A β . In addition, pretreatment with WIN prevented a decrease in copper/zinc-SOD induced by A β _{1–42} (Aguirre-Rueda et al., 2015). Cannabinoid receptor type 2 (CB2) agonist (MDA7) also reduced inflammation and also promoted clearance of amyloid plaques in the transgenic APP/PS1 mice model of AD (Wu et al., 2017). Astroglial hemichannel activity and inflammatory reactions evoked by A β _{25–35} were prevented by



several cannabinoid receptor agonists such as WIN, 2-AG, and methanandamide (Gajardo-Gómez et al., 2017). Pantethine (B5 vitamin precursor) was able to modulate the astrocytic metabolic changes and inflammatory patterns induced by Aβ_{1–42} in astrocytes derived from the 5xFAD transgenic mouse model of AD (van Gijssel-Bonnello et al., 2017). In cultured cortical astrocytes, donepezil was shown to reduce inflammatory responses via nAChR and PI3K-Akt pathway, and to decrease intracellular ROS levels (Makitani et al., 2017). As mentioned early, donepezil is a cholinesterase inhibitor commonly used in AD patients.

Other strategies to reduce OS in AD models involve enhancers of antioxidative endogenous factors. For instance, pelargonidin (estrogen receptor agonist) increases catalase activity, reduces astrocyte activation in the hippocampus after Aβ_{25–35} exposure, and also prevents Aβ-induced spatial memory impairment (Sohanaki et al., 2016). *Bambusae concretio Salicea* treatment increases GSH-S-transferase and prevented catalase, SOD, GPX reduction, induced by Aβ_{25–35} in cultured astrocyte cells (Jeong et al., 2005). The novel compound Monascin is able to activate the expression of several antioxidative genes such as SOD-1, SOD-2, SOD-3, and Hsp16.2, and as a consequence reduced Aβ toxicity (Shi et al., 2016). *In vitro* and *in vivo* studies with exogenous antioxidative compounds such as resveratrol (Wang

G. et al., 2016), tocotrienol (vitamin E form) (Ibrahim et al., 2017), anthocyanins (Rehman et al., 2017), and epicatechin (Cuevas et al., 2009) have shown beneficial effects in AD models. Finally, 3H-1,2-dithiole-3-thione, a potent free radical scavenger, is able to reduce ROS production in the AD cellular model N2a/APP_{swe} (Wang et al., 2017).

CONCLUSION

Neuroinflammation and OS are part of the functional changes frequently observed in the brains of individuals with AD. Aβ has been shown to alter the normal dynamics of both inflammatory and antioxidant and prooxidant balance, promoting an unhealthy state for the brain and neuronal–glial communication networks. Astrocytes are involved in both inflammation and OS regulation in the CNS, and seem to have a central role in the basic pathophysiological aspects that surround this neurodegenerative disease. Although the precise relation between neuroinflammation, OS, astrocytes, and AD is still not clear, the evidence points toward an important participative role of the Aβ/NF-κB interaction in astrocytes as a critical agent in the pathological mechanism of AD. Despite the continuous efforts to develop a successful treatment for AD, there is still a

gap in the knowledge of the precise etiological aspects of this disease which difficult the advance of therapeutics. Therefore, and due to the evidence presented in this review, is important to start considering astrocytes as a valuable novel therapeutic and neuroprotective target for future studies related to the treatment and mechanistic comprehension of AD.

AUTHOR CONTRIBUTIONS

RG-R conceived the review paper. RG-R, MN-M, and KV-S edited the final version of the manuscript. RG-R wrote the section: Introduction. RG-R and MN-M wrote the section:

Astrocytes and Alzheimer's Disease. RG-R and KV-S wrote the section: Neuroinflammation, Alzheimer's Disease, and Astrocytes. KV-S, DA-S, and LM-M wrote the section: Oxidative Stress, Alzheimer's Disease, and Astrocytes. MN-M wrote the section: Novel Neuroprotective and Therapeutic Measures in Alzheimer's Disease. RG-R, MN-M, DA-S, and LM-M were involved in the construction of the figure.

FUNDING

The review was funded in part by Universidad del Rosario.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer ML and handling Editor declared their shared affiliation.

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