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Review

Glial Alterations in Aging and Alzheimer's Disease: A Novel Basis to Understand, Prevent and Treat the Degenerative Process

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Abstract

Neurons, from the time of their birth until their death, are always accompanied by neuroglial cells, maintaining very close morphological and functional relationships among themselves. Classically three main neuroglial families have been considered within the central nervous system (CNS): astroglia, oligodendroglia, and microglia. However, using morphological and immuno-cytochemical criteria, several different types/subtypes of neuroglial cells have been identified, each exerting specific physiological and pathological effects on the neurons. The neuron–neuroglial relationships are quite complex (glio-glial, glio-neuronal, and neuro-glial cell signaling, including glio-transmission), and all these routes of cell communication are essential for supporting brain function. Subtle morpho-functional changes resulting from glial cell plasticity occur in parallel to the plastic neuronal changes that serve to optimize the functionality of neurons and neuronal circuits. Moreover, all the different types/subtypes of neuroglia may adopt a reactive status, referred to as "gliosis", in which novel actions are performed. These latter morpho-functional changes are difficult to understand as they involve both neuroprotection/neuro-repair and neurodegeneration. Diverse and profound regional and local neuroglial changes occur in all the involutive processes [physiological and

pathological aging or neurodegenerative disorders such as Alzheimer´s disease (AD)], although the exact implications of these spatiotemporal modifications for the different neuroglial types are not sufficiently well understood. Owing to all these features, neuroglial cells become elements of paramount importance when attempting to elucidate any physiological or pathological processes occurring in the CNS. Furthermore, in recent years, potential therapeutic interventions capable of positively modifying the responses of neuroglial cells have been proposed to prevent and/or treat degenerative CNS conditions. In the present review, the different neuroglial cells and their responses are discussed in order to understand their possible role in the pathogenesis, diagnosis and treatment (preventive or palliative) of involutive CNS processes. In addition, the existence of differentiated and/or concurrent pathogenic and neuro-protective/neuro-restorative astroglial and microglial responses is addressed.

Keywords
Aging; neurodegenerative diseases; Alzheimer's disease; neuroglial cells; reactive neuroglia; glioplasticity; gliosis; astrogliosis; microgliosis; glial neurodegeneration/neuroprotection

1. Introduction: The History of Glial Cells

The concept of "neuroglia" (or the "nervous cement") was established in 1858 by Wirchow [1], who described an ill-defined "tissue or substance" (involving a matrix and cells) that surrounded neurons. Further studies conducted on this neuronal cement [2-8] re-defined it as a complex set of distinct families/types/subtypes of glial cells that accompany neurons, excluding the presence of extraneuronal substances. Three main families of these cells were finally established: astroglia, oligodendroglia, and microglia [8-12]. Recently, a fourth cell type referred to as $NG2^+$ (neuron-glial antigen positive type 2) cells has gained attention, considered to be "adult oligodendrocyte progenitors" with astroglial and oligodendroglial properties [13-16]. However, it remains unclear whether this is actually a type of oligodendrocyte or another family of the glia cells [13-16].

Several studies in the literature have focused on the types of cells in these three classic families of neuroglia, defining the roles of each of these cells in the nervous system in both physiological and pathological states. Initially, astroglia were considered fundamental for embryonic development [5, 7] and the main mechanical support cells, along with the oligodendroglia [3, 5, 17]. Subsequently, maintaining homeostasis of the nervous system was identified as another important role of these cells [9, 18-20]. However, all types of glial cells are now supposed to be involved in almost all the functions of neurons [9, 10, 18-25], ranging from the most simple to the most complex activities like cognitive behavior. It is considered that the relationship between neurons and glia is so intertwined that the "plastic/adaptative" changes occurring in neurons (neuroplasticity) are intrinsically linked to the "plastic/adaptative" changes in the neuroglia (glial plasticity or glioplasticity), including astroglioplasticity, oligodendroplasticity and microglioplasticity [9, 23, 24]. It is often quite difficult to determine which among the two, the neuron or the glial cell, is the promoter of a physiological neuronal–glial plastic change. Similarly, it is often difficult to specify which cell type (neuron or neuroglial cell) causes a pathological

alteration to the nervous system. All the glial cell types re-model neurons, their connections and the neuronal circuits in which they participate, while the neurons induce changes in the glial cells [9, 25-29]. Indeed, even in pathological situations like infectious diseases, cancer, trauma, etc., neuronal and glial alterations are almost always observed together [20, 30-33]; as also holds true in physiological senility and neurodegenerative disorders. The glial changes occurring in these scenarios are commonly referred to as "gliosis" (astrogliosis, oligodendrogliosis and microgliosis), considering that these cells (or a set of them) are "activated" or that they exhibit a reaction against the harmful situation. In these pathological conditions, "new glial elements with new properties", displaying significant morphological and functional alterations, and modified gene expression (including that of novel genes), may appear in different areas of the nervous system (Figures 1–3) [9, 12].

It is convenient to define the glial adaptative/plastic changes in "normal" scenarios (learning, memory, etc.). However, in pathological scenarios, in which gliosis is the most evident alteration to glia, it is quite difficult to analyze the effect on neurons. Glioplasticity may be observed as a neuroprotective process and gliosis as an excessive response of glial plasticity. These alterations in gliosis may produce different and contrasting effects on the neurons, such as neuroprotection or neurotoxicity [9, 12]. For instance, glial cells may simultaneously produce pro-inflammatory and anti-inflammatory factors that "drive" either neuroprotection or neurodegeneration [25, 29, 34].

In recent years, several studies have highlighted the involvement of glial cells in aging, Alzheimer´s disease (AD) and several other neurodegenerative diseases, increasing the understanding of the pathogenesis of these processes. Astrogliosis and microgliosis are the key processes according to the latest theories on these forms of CNS involution, and it is now believed that neuroglial cells may serve as a suitable target in neurodegenerative therapy. However, the exact role of the different glial cells in each pathogenic phase of these conditions is far from being fully understood.

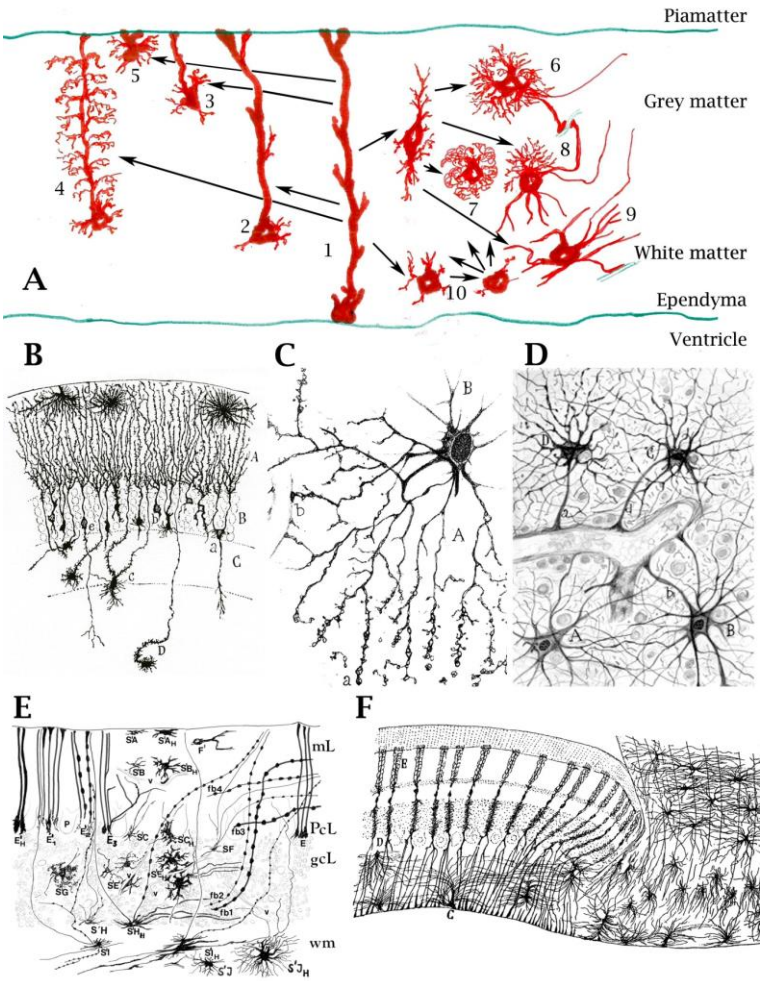

Figure 1 Astroglial cells and specific cell types/sub-types in different regions of the brain. A) Scheme of the different astroglial cell types and their relationships. 1- Radial ependymal stem cell or tanycyte possessing a long process that terminates at the pia-mater. In adult mammals, the presence of this astroglial cell type is restricted to the periventricular centers, and it may give rise to other cell types [9]. 2, 3, 4- Radial astrocytes that form palisades of processes that project to the pia-mater (2, 3- in the hippocampus; 4- "epithelial Golgi cells", producing Bergmann fibers with laminar appendages in the cerebellum). 5- Subpial astrocyte. 6- Protoplasmic astrocyte in the gray matter. 7- Velate astrocyte with laminar appendages, typical of the cerebellum. 8- Mixed protoplasmic–fibrous astrocyte in the gray matter. 9- Fibrous astrocyte in the white matter. 10- Astrocytic stem cells that possibly develop into different types/subtypes of astrocytes, as well as into neurons or oligodendrocytes. B-E) Cajal's drawings of astroglial cells: B) Tanycytes, radial astrocytes and protoplasmic astrocytes from the cerebellum of a new-born rabbit [2]. C) Mixed protoplasmic–fibrous astrocyte [5]. D) Fibrous astrocytes in the white matter [5]. E) Radial and protoplasmic astrocytes in the hippocampus [4]. F) Different types/subtypes of radial (Bergmann), protoplasmic (SA-SH) and fibrous (SI-SJ) astrocytes from ref. [12]. Long glial processes (smooth and varicose) are also depicted. Normal and hypertrophic ($_{-H}$) cells are represented.

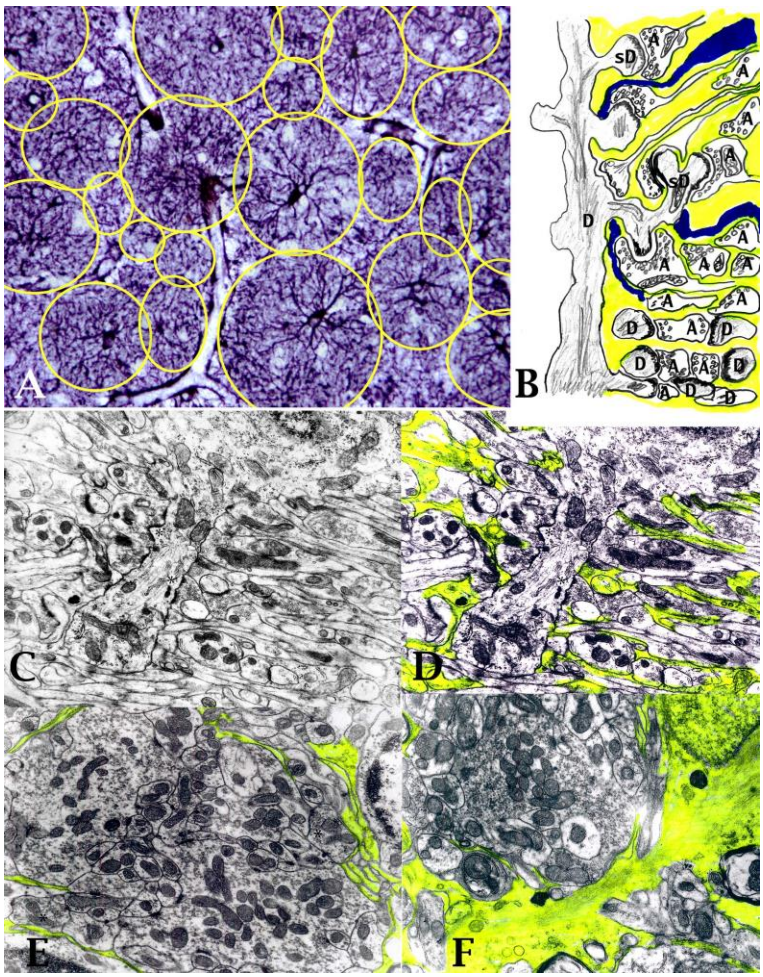

Figure 2 Astroglial processes. A) Protoplasmic astrocytes in the frontal cortex of an AD patient (using GFAP immunocytochemistry, no H/E staining). The astrocyte processes cover an area of the neuropil. The areas covered, and the number, size and shape of the processes vary, suffering dynamic short-term to long-term pathophysiological changes that induce changes in the neurons and neuronal circuits. The thinnest astrocyte appendages surround the complex synaptic connections (dendrite–axonal endings). Thin glial processes are observable only at the Electron Microscope level (B, scheme; glial processes depicted in yellow). C-F) Electron Microscopy images of rat cerebellar cortex. In C and D, the appendages of Bergmann fibers (depicted in yellow in D) are evident among the parallel fibers in the molecular layer. E) Thin astrocyte processes surrounding a glomerullum of the granule cell layer in a 6-month-old rat. F) Hypertrophic astrocyte processes surrounding a glomerullum in a 30-month-old rat. (A, 40x; C-F, 20,000x; A, Axon; D, dendrite; sD, dendritic spine).

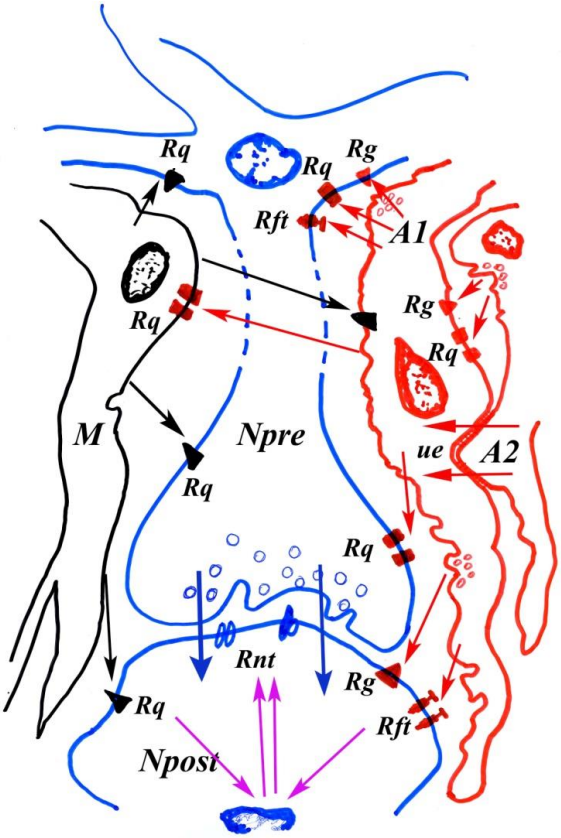

Figure 3 Scheme of the integration of different glio-neuronal cell communication systems (including gliotransmission) in neuro-neuronal communication. Pre-synaptic (Npre) and post-synaptic (Npost) neurons establish synaptic communication mediated by neurotransmitters (blue arrows). In most cases, neurotransmitters are stored in synaptic vesicles and when released, they act on specific receptors in the post-synaptic membrane (Rnt). The synapse is ensheathed by the glial processes of astrocytes (A) and microglia cells (M) that release cell messengers (such as neurotrophic factors that activate neurotrophin receptors Rft, or cytokines, chemokines, prostaglandins, NO, etc., which activate specific Rq receptors). These messengers cause changes in both pre-synaptic (soma or synaptic boutons) and post-synaptic regions. The changes are mediated through the activation of intracellular second-messenger pathways (or cell signaling pathways), such that the synaptic response to the neurotransmitter is modulated by the local changes in glio-neuronal cell communication at the synaptic level. It is also evident that glial cells, particularly astrocytes, are capable of producing "gliotransmitters" that activate synapses, acting on specific receptors (Rq) and producing activation or inhibition of the neuronal membranes. Through astrocyte "gap junctions (ue)", neuro-active molecules circulate and are released close to the synaptic sites. The intracellular signaling pathways for neurotrophic factors, as well as the pathways related to cytokines and chemokines, are capable of producing a wide variety of cellular and molecular effects, ranging from the activation or inhibition of enzymes and several other molecules, to the activation or inhibition of different genes. Therefore, the modulatory effects may be manifested relatively rapidly and for shorter or longer periods of time; adapted from an earlier study [35].

2. An Overview of Neuroglial Cells, their Responses and their Implications on CNS Functions

2.1 Astroglia

2.1.1 Cell Types and Functions

Numerous different neuroepithelial cell types and subtypes in close association with neurons are considered to be astroglia (in a morphological and functional sense) (Figure 1) [9, 12, 18, 36]. Astrocytes adopt various morphologies in the CNS, ranging from projecting one or a few long parallel processes toward the pia-mater to adopting a stellate morphology with several short and a few long processes. These morphologies may be region specific [9, 12] (Figure 1), and indeed, a specific astroglial cytoarchitecture is one of the main features of most CNS regions. Moreover, higher astrocyte densities may arise in certain areas of the brain, such as around the cortical barrels or in the transition areas between the different layers of the hippocampus and the cerebellum [12]. Indeed, different subtypes of astroglia may be identified using cytochemical or biochemical methods, and also on the basis of morphology (Figure 2). GFAP immunostaining is the most widely used technique to determine the presence of astrocytes in brain sections, although several astroglia do not contain GFAP [2, 12]. Aldehyde dehydrogenase is another marker for astrocytes, although only a subset of astrocytes with this enzyme is GFAP-immunopositive [24, 34, 37-40]. Glioplasticity, the physiological adaptation that optimizes astrocyte responses to both normal fluctuations in the internal milieu and the signals from outside the brain [12, 20], alters the genes expressed by certain types of astrocytes, in addition to altering their morphofunctional structure and their active biochemical pathways. Therefore, in certain physiological situations, the study of astroglial modifications may be difficult.

During prenatal development and the establishment of neuronal circuits, astroglia cells are involved in neurogenesis, neuron migration and axon guidance [4, 7, 19]. In postnatal development, these cells form a very complex astroglial network, surrounding neurons and connecting them with blood vessels, as well as participating in the configuration of specific synaptic contact areas (microdomains, glial compartments, glial territories, or astroglial cradles) (Figure 2–4) [18, 19, 30, 41-46]. In the vicinity of synaptic complexes, an astrocyte's perisynaptic processes change their morphology (size and shape) and function (secretion of neuroactive factors and regulators of neurotransmission) [47], serving as an essential functional component for synaptogenesis, and contributing to the maintenance of synapses, synaptic connectivity, synaptic plasticity and information processing in the CNS [43]. Human astrocytes exhibit remarkably higher complexity than astrocytes in other mammals and they are involved in a greater number of synapses [43]. The intertwined and dynamic astroglial–neuronal relationship is highly complex. It involves multiple processes (neuro-glial, glial-neuronal, neuro-neuronal and glial-glial cell communication) mediated by a large number of different substances, such as neurotransmitters, neurotrophins, chemokines, cytokines, prostaglandins, ions, NO and free radicals, among others [9]. The receptors for these substances and their intracellular second messenger pathways are particularly important during the regulation of synaptic function at these levels, with significant implications in physiological and pathological phenomena (Figure 3) [9, 18, 29, 48, 49]. Astrocytes are indispensable for glutamatergic and GABAergic neurotransmission [43, 50]. Moreover, active "glial-transmission" between astrocytes and neurons occurs through specific gliotransmitters,

which are either excitatory (glutamate, aspartate, serine, eicosanoids, ATP and excitatory proteins) or inhibitory (adenosine and inhibitory peptides) (Figure 3) [2, 50-54].

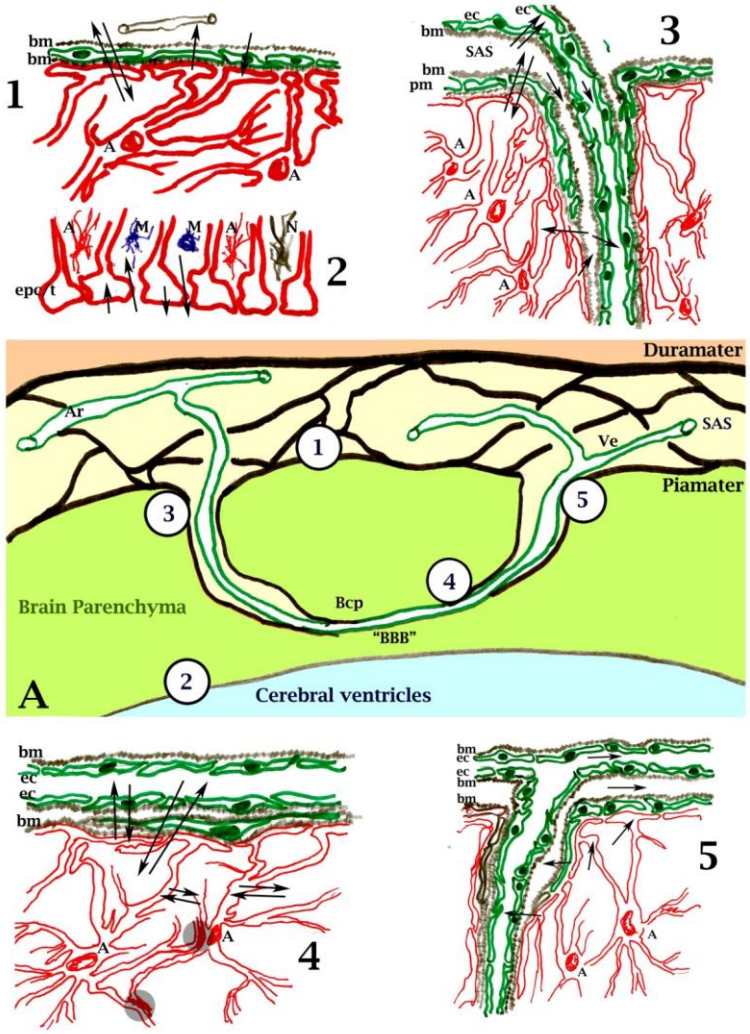

Figure 4 Scheme of the relationships between the CNS and the body biofluids, highlighting the morphofunctional importance of astroglial cells (see text for explanation) [9, 55]. Specific barriers separate the brain parenchyma from the body's biofluids. The pia-arachnoid (1) and ventricular (2) brain barriers form the limits to the spaces occupied by the cerebrospinal fluid (CSF)–the sub-arachnoid space (SAS) and the brain ventricles, respectively. A unique barrier may be defined in the Virchow-Robin spaces (VRS) located around the arterioles (3) and venules (5) that perforate the brain; these barriers are defined by the basal membranes of the glia, pia and endothelium, and terminate at the capillaries present at the joining of the basement membranes of glia and the endothelium. Whether the SAS and the VRS are anatomically separated via a pial membrane or not remains unclear. At the level of the brain capillaries (Bcps), the "blood-brain barrier" (BBB; 4) is a specialized and complex morphofunctional structure that restricts the access of the blood to the brain. The BBB is based on a specific cell structure involving a "non-fenestrated" endothelium, a specific basal membrane and a continuous sheathing of unique astroglial processes/vascular feet, as well as on the special permeation and diffusion properties

of substances that restrict their flow between the brain parenchyma and the blood. Astroglia fulfill important morphological and functional roles at all these barriers in relation to the fluid and solute flux between the brain parenchyma and the CSF or the blood (arrows). Ar, artery; A, astrocyte; SAS, sub-arachnoid space; Bcp, blood capillaries; BBB, Blood-Brain Barrier; bm, basal membrane; M, microglial cell; ec, endothelial cell; pm, pial membrane; Ve, vein; epc/t, ependymal cell/Tanycyte.

CNS homeostasis is maintained mainly by the astroglial cells through different mechanisms and morphofunctional pathways. These cells provide metabolic support to neurons and they also drain toxic substances from the CNS–parenchymal interstitial space. Astrocytes establish a unique relationship with blood vessels through specific processes (vascular end-feet) and other elements (the glia limitans); they also have a unique relationship with the pial border (Figure 4) [9]. Specific barriers separate the brain parenchyma from the body's biofluids. The pia-arachnoid (Figure 4–1) and the ventricular (Figure 4–2) brain barriers form the limits to the spaces occupied by the cerebrospinal fluid (CSF) – the sub-arachnoid space (SAS) and the brain ventricles, respectively. A unique barrier may be defined in the Virchow-Robin spaces (VRS) located around the arterioles (Figure 4–3) and venules (Figure 4–5) that perforate the brain. These barriers are delineated by the basal membranes of the glia, pia and endothelium, and they terminate at the capillaries at the joining point of the basement membranes of the glia and endothelium. At the level of the brain capillaries (Bcps; Figure 4–4), a unique and complex morphofunctional structure named the "blood-brain barrier" (BBB) is formed, which limits the access of the blood to the brain. The BBB is based on a specific cell structure that involves a "non-fenestrated" endothelium, a specific basal membrane and a continuous sheathing of special astroglial processes (vascular feet). In addition, the permeation and diffusion of substances between the brain parenchyma and the blood are strictly restricted [55]. Parenchymal endothelial cells (ECs; Figure 4–4) are sealed by means of adherens and tight junctions with high electrical resistance, low permeability to polar solutes and a low rate of transcytosis. These ECs express various specific solute carriers, ion channels and transporters that allow the passage of water, solutes and larger molecules in a complex and specific manner, which is not yet completely understood.

Astroglial cells fulfill an important morphofunctional role at all these barriers, particularly in relation to the fluid and solute flux between the brain parenchyma and the CSF or the blood. Astroglial cells may transport substances (arrows in Figure 4) to and from the CSF and the blood, or through the parenchyma, in the following ways: cell-to-cell, through gap junctions (red circles in Figure 4–4), cell-to-extracellular space or cell-to-cell via aquaporins, and cell-to-blood or cell-to-cell via specific mechanisms to pass through the ECs and the basal membrane.

The VRS facilitates the bi-directional fluid exchange between the brain extracellular space and the SAS, as well as the para-arterial and para-venous drainage of fluid, solutes or various molecules to the lymphatic system at the exterior base of the skull. Glia control fluid exchange at the level of the VRS, which forms the basis for a "glymphatic" pathway, which connects arterial and venous VRS, and also involves astrocytes [9, 55, 56]. This pathway is important in AD because the clearing of toxic substances from the brain (amyloid and cytokines) is impaired in this neurodegenerative disease. It is supposed that the CSF from the SAS enters the brain through paravascular channels surrounding the penetrating arteries, it is exchanged with the brain extracellular fluid and thereafter, it is cleared to the paravascular spaces surrounding the draining

veins, thereby exporting different solutes. Astroglial water transport via aquaporins (AQP4) expressed exclusively in the perivascular astrocytic end-feet facilitates this flux, and a mislocalization of AQP4 from the perivascular end-feet to the rest of the astrocytic processes disrupts this efficient interstitial flow. The failure of glymphatic interstitial solute clearance may contribute to the post-injury deposition of extracellular and intracellular protein aggregates (such as β-amyloid, Aβ or tau) [55-61]. At the VRS level, blood cells (macrophages and lymphocytes) may enter the brain parenchyma, an important step in the pathogenesis of neurodegenerative diseases.

2.1.2 Astrogliosis

The plasticity of astrocytes is based on fluctuating, and subtle, morphological and functional alterations, which allow these cells to adapt to the requirements of neurons and neuronal circuits. In more complex physiological situations, such as senility, or in pathological states such as trauma, toxicity or infection, as well as in neurodegenerative diseases, astrocytes undergo further profound alterations which may be classified under the term “astrogliosis” [12, 20]. The concept and scope of astrogliosis have been discussed widely in the literature, and our research group has also attempted to elucidate this concept previously [9, 62]. In astrogliosis, morphological alterations to the astrocyte cell body and processes are observed, as well as changes in its GFAP immunoreactivity, although these changes are not the main or the only alterations that define astrogliosis. A few years ago, astrogliosis was defined as astroglial hypertrophy, hyperplasia and hyperproduction of gliofibrils [3, 9, 63], and it was considered to be related mainly to senility and pathological conditions (Figure 1) [2, 5, 9, 12, 64, 65]. However, this reactive process was recently described as a constitutive, graded, multi-stage and evolutionarily-conserved defensive astroglial reaction [42]. This latest definition of the process highlights that while the reactivity of astrocytes might be harmful to the surrounding nervous tissue, it may provide neuroprotectivity or serve as a reparative mechanism in damaged nerve tissue [9, 62].

Currently, the feature of gliosis that is considered most important is hypertrophy or the enhanced production of glial fibrils, irrespective of whether hyperplasia occurs or not (Figure 2) [9, 66]. However, the accuracy of GFAP immunoreactivity in determining the level of astrogliosis is debatable due to the co-existence of immunonegative normal and hypertrophic cells, and due to the presence of glial processes in pathological and reparative nervous tissues [9, 12, 39, 67]. In order to understand the "astrogliosis" that occurs in different involutive or reparative processes throughout the CNS, it is necessary to analyze the different types of glia that exist, the glial disorganization associated with the specific cytoarchitecture of a particular region, and the morphofunctional responses of each astroglial subtype. Certainly, the distinct "patterns" of astrogliosis associated with different involutive/degenerative or reparative processes in the different regions of the CNS might have important pathogenic and therapeutic implications (Figure 5) [12].

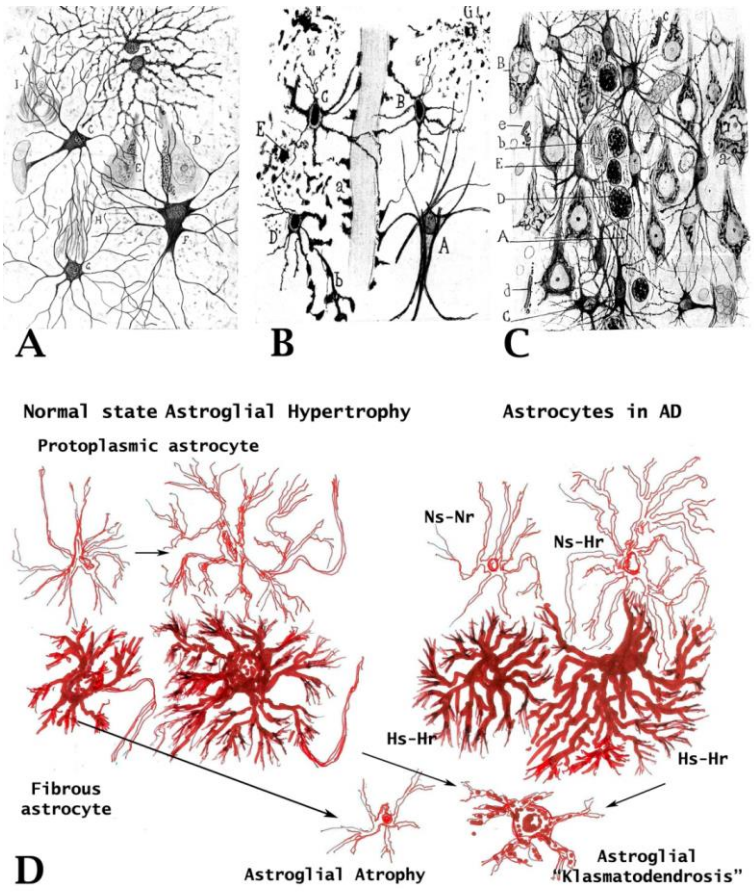

Figure 5 Reactive astrocytes. A) Achúcarro and Gayarre's drawing depicting gliosis in the hippocampus of a brain with "senile dementia" [64, 65]. In this drawing, protoplasmic and fibrous astrocytes (C, G, F) are depicted in association with damaged neurons. B) A drawing illustrating different subsets of reactive protoplasmic and fibrous (B) astrocytes (B, D), and those of "involutive astrocytes" (F, G) secondary to a degenerative phenomenon, referred to as *"Klasmodendrosis"* by Cajal and Achúcarro, in the case of progressive general palsy [2]. C) Astroglial cells exhibiting the process of *"klasmodendrosis"* in AD (GFAP immunostaining, no H/E). D) Scheme of different types of reactive astroglia according to both silver impregnation and GFAP immunostaining. Protoplasmic and fibrous astrocytes may undergo distinct reactive changes in shape, size and GFAP content. In senility, neurodegenerative diseases (such as AD) and other degenerative situations in the CNS, different types of GFAP astrocytes may be observed, such as normal size-normoreactive (Ns-Nr), normal size hyperreactive (Ns-H), hypertrophic-normoreactive (H-Nr), and hypertrophic-hyperreactive (H-H). In addition, GFAP-immunonegative, atrophic and degenerative (consecutive to a process of *Klasmodendrosis*) astrocytes are observed.

What Factors Induce Astrogliosis? Several possible factors may cause astrogliosis: noxious agents, such as infectious and toxic agents or even medicines; traumatic, anoxic or excitatory conditions that induce cell damage (neuronal and/or glial), in which glioreactive substances and/or cell debris are produced; and inducers of glial reactive processes from systems external to the

brain, such as metabolic alterations, etc. However, one may also consider the various astroglial pathologies that have been studied to a limited extent to date and that are associated with altered gene expression, similar to the events that occur in neurodegenerative diseases [68].

What Factors Mediate the Effects of Astrogliosis? In senility and neurodegenerative diseases like ischemia, AD, Parkinson´s disease (PD), multiple sclerosis (MS), etc., astrocytes release important cytokines (IL–1, IL–6, TNF, etc.), all of which are considered pro-inflammatory factors and that produce neurodegeneration and/or cell death. Neuroprotective/reparative" astrogliosis is mediated by trophic factors (GDNF, Astroglial Factor, etc.), antioxidants (glutathione) and gliotransmitters, among other factors. Several proteins secreted by astrocytes exhibit dual (positive or negative) effects in the different scenarios encountered by reactive astrocytes. Perhaps, the best-studied substances are GFAP and the vimentin of intermediate filaments; in certain experiments, these have been observed to assist neuronal recovery and axon growth, while in other cases, the increase in GFAP parallels neurodegeneration [68].

What are the Effects of Involutive/Neurodegenerative Astrogliosis in the CNS? In different studies conducted on human pathologies using experimental models, different kinds of astroglial responses have been reported. In addition, specific features that might assist in better understanding the pathological processes and in developing glial therapies were identified. The most important ones among these responses and features are:

- In the aged normal CNS, in AD and in several other pathological situations [12, 66, 69], the coexistence of different classes of GFAP-immunoreactive cells (normal size/normo-reactive, normal size/hyper-reactive, and hypertrophic/hyper-reactive) with GFAP negative cells is common (Figure 5). Hyperplasia (newly-formed astrocytes) and an increase in the number and/or length of the processes of astrocytes have also been observed [12]. Two possible explanations, which are not mutually exclusive, have been provided for this situation: a) there might exist different sets of the same astrocyte subtype exhibiting different GFAP-immunoreactivities, and possibly having different functions; b) astrocytes are highly dynamic cells that transform from a resting to a reactive state, and vice versa, and that this process is regulated by neuronal and glial (astroglial or microglial) factors [12, 66, 69].
- Complex and region-specific age-related changes in the astroglial markers suggest that astrocytes undergo a complex, age-dependent, region-specific remodeling inside the brain [70]. Astrogliosis is usually stronger in layers I and II of the cerebral cortex, and in the transition zones between the layers of the cerebellar cortex and the hippocampus (molecular-neuronal layers, which form the borders of the white matter) (See below) [12].
- Homogenous, "generalized" astrogliosis may be observed in different regions of the CNS, both in experimental and pathological situations, without hyperplasia or significant glial architectonic alterations (for instance, following pilocarpine intoxication). However, in most pathological or lesioned tissues, astroglial responses appear to be heterogeneous, as if the responses of each astrocyte are "individualized". Moreover, in certain areas, hyperplasia also occurs in association with astrogliosis. In most pathological processes, it is difficult to delineate a characteristic pattern, as the larger or smaller areas of gliosis are intercalated with the areas of normal appearance, or a mosaic of astrocytes may form in the areas with varying degrees of hypertrophy, dystrophy and atrophy (Figure 5). Various explanations are provided in the literature for these disorganized or individualized glial responses, including a differential response by the different astroglial subtypes or subsets, uncoordinated responses

from the neuro-glio-vascular units in that region, and local environmental changes, among others. [12]. Nevertheless, focal responses may overlap, affecting a large number of neurons and their connections in various ways.

- Foci of intense astrogliosis may exist in selected regions of the hippocampus, brain and cerebellar cortex of senile or AD brains and under the influence of other neurodegenerative processes. Numerous reactive astrocytes or coalescences of hypertrophic astrocytic processes may create "astroglial spaces" in the neuropil (Figures 5 and 6) [12, 70].

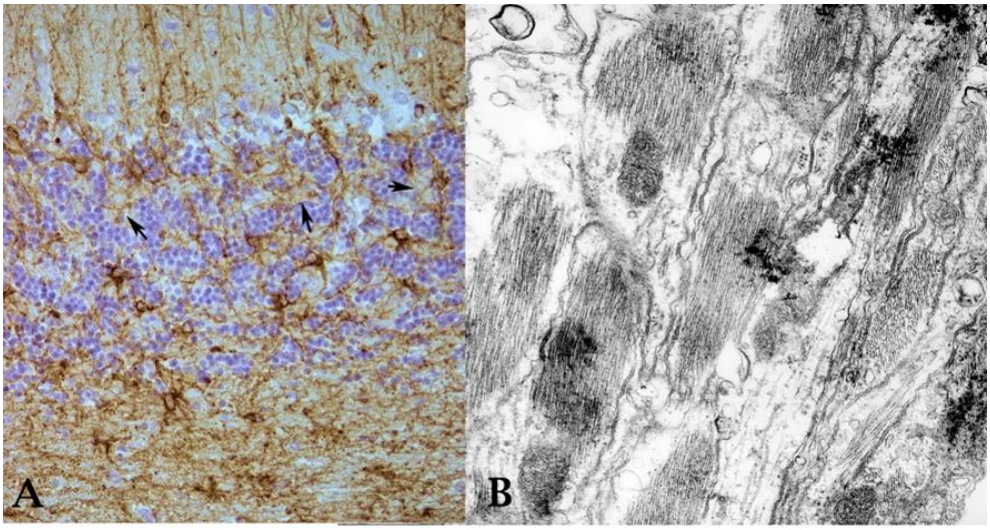

Figure 6 "Astroglial spaces" created by coalescent astroglial processes in senility and neurodegenerative diseases. A) The cerebellum of an AD patient. GFAP-immunostained spaces (arrows) between cells in the granule and in Purkinje cell layers. GFAP immunostaining and H/E contrast (optic microscopy, 30x). B) Cerebellum of a 30-month-old rat. Astroglial space created by the coalescence of several thin astroglial processes, exhibiting dense gliofibril content (Electron microscopy, 30,000x).

In special situations, hypertrophic astroglial elements from one layer may invade others that are generally not reachable (for example, cerebellar velate astrocytes invade the Purkinje cell and molecular layers). The disruption of such layers appears to be an important sign of involution in the CNS. Cajal observed that neurons from one layer, when present ectopically in another layer, are generally surrounded by hypertrophic glial cells [4]. Notably, at certain times, different types of large hypertrophic-hyperactive elements coexist, although not necessarily, with other neuropathological markers (such as amyloid deposits, dystrophic neurons or neurites). The reason for the coexistence of different types of gliosis remains unknown to date, although this coexistence reflects the specific architectonic aspects of the layers and regions of the brain, the different neuronal, glial and extra-CNS factors that induce glial responses in these zones, and the distinct responses of the different types of astrocytes (including hyperplasia).

Local injury (traumatic, toxic, infectious, etc.) affecting a relatively extensive area of the CNS induces a rapid astroglial reaction of varying intensity depending on the type of vascular injury, the degree of anoxia/hypoxia, and that of neuronal and neurite dystrophy, as well as homeostatic changes in the region, etc. (Figure 7) [71]. In a short period of time, a central area is established, which usually becomes necrotic, along with a peripheral area (the "threshold" zone) in which

regeneration may subsequently occur; the latter area promotes functional recovery in the damaged region. Astroglial cells in the peripheral zone act sequentially to recover homeostasis, neurotransmission and neuronal metabolism, and to remove cell debris. In several regions, hypertrophic astrocytes accumulate and persist over time, forming a "glial scar" that serves as a reminder of the injury [72]. The changes that occur in astroglial cells in the central and peripheral areas of each lesion, both at early and later stages, vary as the lesion evolves, resolving the problems encountered by the surviving neurons or leading to the removal of damaged tissue [72]. If not resolved in time, reactive gliosis could exert inhibitory effects on neuronal adaptation and recovery, becoming a source of neuropathology [9]. Besides the reactions occurring in the lesion area, astroglial changes may also be observed in other proximal or remote areas connected synaptically or vascularly [63].

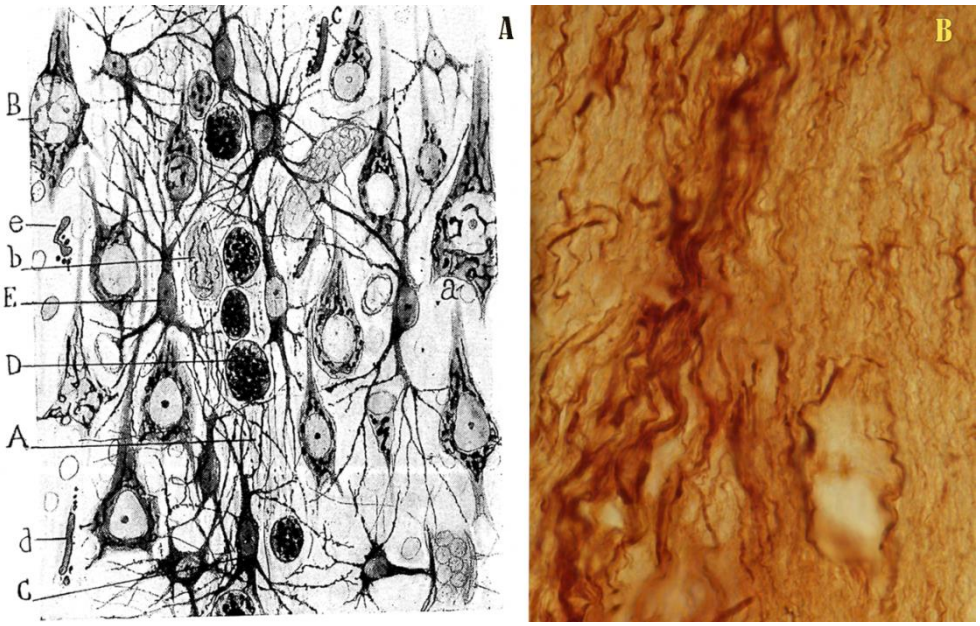

Figure 7 "Astroglial scars" formed by coalescent astroglial cells and processes following CNS lesion. A) Cajal's drawing [2] of a glial scar formed after a traumatic lesion, displaying hypertrophic astrocytes and other glial cells with unstained processes (microglial cells) in close association with damaged neurons. B) Astroglial scar formed by the coalescence of strongly GFAP immunoreactive processes in the frontoparietal cortex of a rat, in the region where a stereotaxic injection needle crossed six months ago. GFAP immunostaining, no H/E contrast, 100x.

Functions of Astrogliosis. As discussed earlier, astrogliosis must be considered a dual process–degenerative (in most scenarios) as well as neuroprotective or reparative [9, 62]. The long term presence of reactive astrocytes in pathological situations suggests that these cells exert a detrimental effect on the nervous system, long after injury or infection. Moreover, the presence of astrocytes, even when there are signs of tissue repair, indicates that these cells also exert a neuroprotective/reparative effect. Indeed, it is possible that both these effects coexist in the brain, owing to the presence of different groups of astrocytes performing different functions, and because distinct toxic or reparative factors may reach different regions where astrocytes are also present. It has been proposed that sequential spatial and/or temporal responses may be produced

with the sole objective of repairing the nervous tissue, although these may or may not be successful. Initially, the responses aim to remove the critically damaged neurons and recover those that are less damaged, although excess vigor in the reparative response may contribute to the spread of injury and cause permanent involution of the tissue. The most well-known examples of this are based on the study of focal lesions in the nervous system (traumatic, anoxic and stroke). Cell death occurs at the foci of such damage (neuronal and glial), immediately inducing inflammatory astrogliosis that eliminates the damaged tissue in collaboration with microgliosis.

In areas peripheral to the lesions, where cellular alterations may also be observed although a restorative process occurs, reparative astrogliosis is produced. This reactive astrogliosis induces medium to long-term recovery of neurons and neuronal circuits, achieving a level of activity similar to that possessed previously. In the long term, permanent signs may exist, involving the accumulation of hypertrophic astrocytes that isolate the remains of the damaged tissue (glial scar). When the formation of glial scar is initiated, astrocytes that produce trophic factors associated with neuronal repair may be observed [62, 73], which also induce revascularization and normalization of homeostasis in the affected region of the nervous system [9].

2.1.3 Astroglial Involution

Astrocyte "senescence", atrophy and dystrophy have been reported in several conditions [9, 31] (Figure 5), and although poorly understood to date, involution of the astroglial cells was described many years ago by Achúcarro and Cajal [2, 64, 65]. These authors termed the degeneration of hypertrophic astrocytes as "*klasmodendrosis*" (or Klasmatodendrosis). This pathological process could be linked to neurodegenerative diseases. Klasmodendrosis is defined as the involution of astroglia, and it is characterized by the regression of their cell body, pyknosis of their nucleus and, most importantly, the regression/degeneration of the glial processes that appear to fragment. This may be observed in greater detail using classic silver impregnation, which allows the degenerated glial processes that have become disconnected from their cell of origin to be visualized. Astrocyte "senescence" is characterized by an excessive production/accumulation of toxic products (e.g., IL–8, angiogenin, MMP–3, MMP–10, and TIMP2) and reduced levels of IL–10 [74, 75].

2.2 Oligodendroglia

2.2.1 Cell Types and Responses

Since the early works of Del Rio-Hortega, these glial cells of neuro-epithelial origin are generally accepted to be responsible for the myelin sheaths that coat CNS axons [11]. Using novel staining techniques, Rio-Hortega first described a set of glial cells that were not astrocytes, and that he subsequently defined as oligodendrocytes and microglia cells. However, several oligodendroglia subtypes that do not produce myelin are known to provide metabolic neuronal support. While the importance of myelinating cells in the physiology and pathology of the CNS is unquestionable, the role of these non-myelinating cells in pathological processes has not been adequately studied [76]. In recent years, a well-characterized, non-myelinating oligodendrocyte was identified ($NG2^+$ cells), often considered a novel oligodendrocyte subtype (*adult oligodendrocyte progenitor-OPCs-* or synantocyte) and a novel class of glia, or the *fifth element of the nervous system* [47]. These OPCs-

cells may be subdivided into several subtypes with astroglial and oligodendroglial properties, although instead of expressing GFAP they express the NGD chondroitin sulfate proteoglycan [9].

2.2.2 Oligodendrogliosis and Oligodendroglial Involution

Although demyelination appears to be a fairly generalized phenomenon in the pathogenesis of several CNS disorders, oligodendrogliosis in the involutive processes has not been adequately studied to date. In several neurodegenerative diseases and their models, activation of $NG2^+$ cells is observed after neuronal damage, demyelination, astrogliosis and microgliosis, and this is probably related to the production of neuronal and glial pro-inflammatory cytokines [16]. $NG2^+$ cells may differentiate into mature oligodendrocytes, which upregulate the expression of myelin proteins and they form new membrane sheaths around the axons by increasing the number and complexity of their processes [15]. Aberrant myelination occurs in certain brain areas in association with aging and certain degenerative conditions of the CNS. However, there is limited knowledge regarding the behavior of non-myelinating oligodendrocytes, even though a few alterations to these cells are supposed to occur in pathological situations [17]. Remyelination by different glial cells may also be observed in several neurodegenerative processes [77, 78].

It is noteworthy that, as stated earlier in the section describing astroglia, oligodendrocyte progenitor cells (OPCs or $NG2^+$ cells) are capable of undergoing similar involutive "senescence". The senescence-like phenotype of $NG2^+$ cells exhibits a characteristic upregulation of p21, p16 and senescence-associated galactosidase activity in the brain of patients with AD, as well as in an AD mouse model APP-PS1 [79]. Cell senescence is now recognized as an important mechanism associated with a wide range of neurodegenerative human diseases [79-81], with senescent cells exhibiting a senescent-associated secretory phenotype [79, 82] and a pro-inflammatory paracrine effect. Therefore, senescent cells are capable of inducing neurodegenerative changes. Various scenarios may arise in which neuronal toxic products (like Aβ and phospho-Tau) or glial pro-inflammatory cytokines induce senescence in certain cell types, following which senescent cells enhance the pro-inflammatory scenario, thereby accelerating neurodegeneration [81, 83]. Therefore, impeding cellular senescence and/or eliminating senescent $NG2^+$ cells may represent a preventive therapeutic strategy in AD and other neurodegenerative diseases, as discussed below [79, 81, 82].

3. Microglia

3.1 Cell Types and Responses

This family of neuroglial cells differs greatly from the other two owing to its mesodermal origin and its involvement in innate immunity [8, 84-86]. The production of key inflammatory molecules (cytokines, chemokines, and their receptors) during the initiation and progression of all pathological processes has led to microglia being considered the main defense element of the CNS (the "innate immune surveillance" system) [22, 33], and the basis of most of the neuropathological cascades that produce brain diseases. The activation of microglia induces "neuroinflammation" [9, 31, 48, 85-89], a pathophysiological neuroprotective process that may, on occasion, become pathological (Figure 8–10).

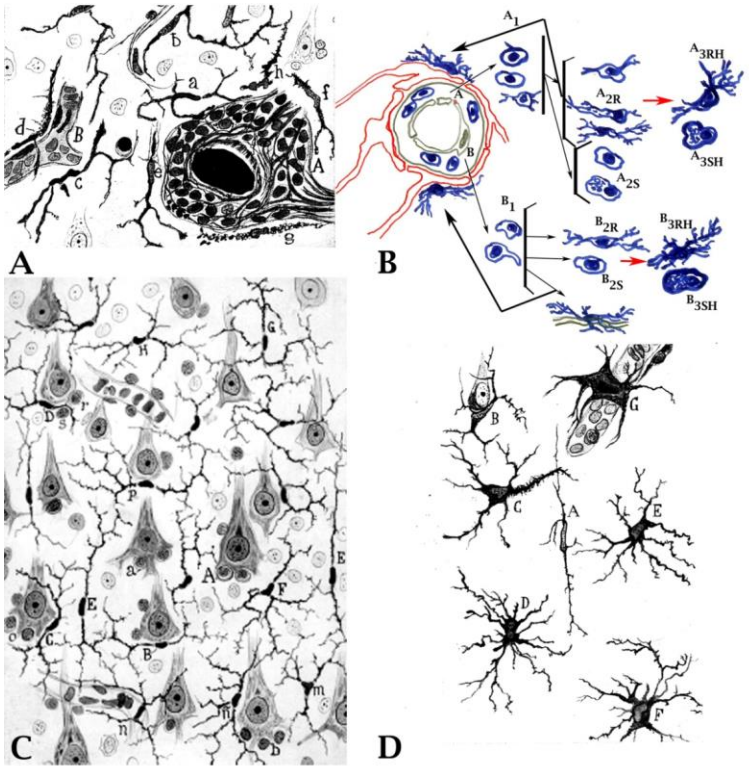

Figure 8 Microglial cells and microgliosis. A, B, C) Cajal's drawings of normal and reactive microglia [4, 72]. A) The "nodule perivasculaire de infiltration"–monocyte/macrophages in the Virchow-Robin spaces; a, e, f, h = ramified microglial elements; g = phagocytic microglia; b, d = a perivascular microglia. B) Different types of ramified microglial cells (A–fusiform; B–perineuronal; C, D, E, F–star-like ramified microglial cells; G–perivascular (hypertrophic) cell. C) Cerebral microgliosis: cortical inflammation as a consequence of a traumatism [72]. D) Scheme of different types of microglial cells in the CNS and the possible relationships among them. In the early stages of embryonic development, yolk sac-derived macrophages either colonize the CNS (A) and differentiate into microglial cells with branched processes, or maintain a non-branched (rounded) aspect, spreading throughout the parenchyma or remaining attached to the blood vessels. Different elements exhibit a certain amount of hypertrophy in their processes when activated in order to cope with the changes in the environment, while the others become round (9 and 10), a shape representative of a phagocytic nature. Stem cells that divide in pathological situations (microgliosis) persist throughout adulthood. Moreover, newly-formed "invading" microglia derived from the monocytes/macrophages generated in the bone marrow are released during neuro-inflammatory events as a result of induction by various factors (such as infection, lesion, neurodegenerative diseases, senility, etc.). The monocytes permeabilize into perivascular Virchow-Robin spaces (B), and subsequently enter the CNS parenchyma, where they could be transformed into microglial cells with different shapes and phenotypes through astrocyte induction.

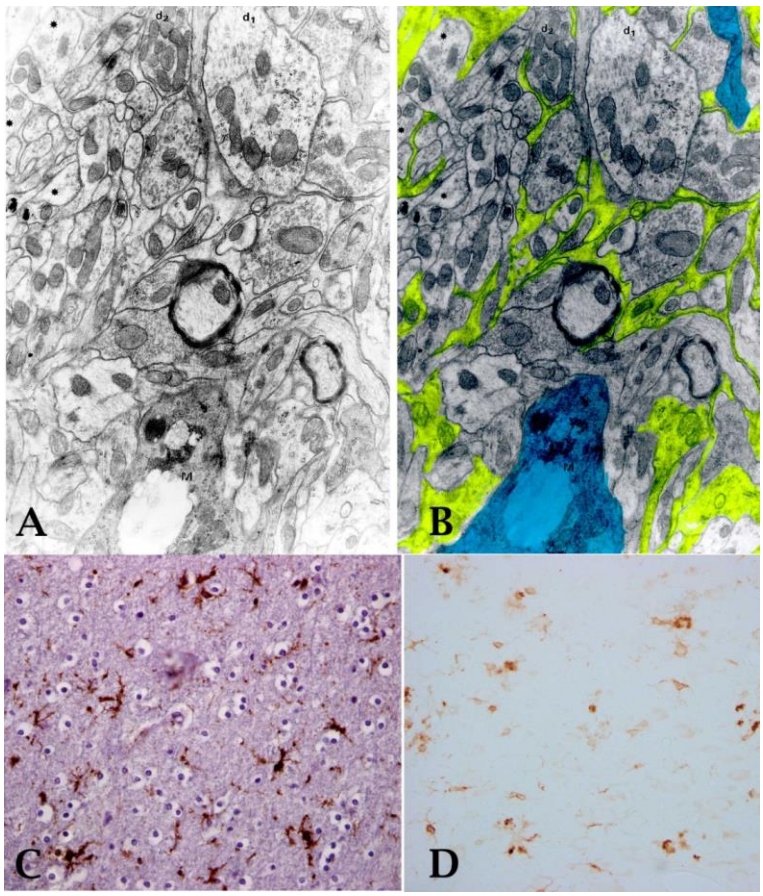

Figure 9 Hypertrophic microglia. A) Electron microscopy image of a round phagocytotic microglial cell (below). B) Electron microscopy image of the thick process of a branched microglial cell (at the top of the micrograph) in the cerebellum of a senile rat. The microglia are depicted in blue (30,000x). C) Ramified microglia from an AD patient; Iba immunostaining; 40x. D) Round and ramified microglia from an AD patient; CD–48 immunostaining; 40x.

On the basis of their origin, two types of microglial cells exist. At the early stages of embryonic development, the yolk sac-derived macrophages colonize the CNS and differentiate into adult microglial cells [9], which ultimately reside in the neuropil or along the blood vessels. This type of *"resting" (resident*) microglial cell remains fixed in its location, although their processes are continuously modified through growth or retraction, supporting their surveillance activity in the normal brain [33]. In pathological situations, these cells may become reactive via microgliosis [90, 91]. The other type of microglia is the "*invading*" microglia, generated from the monocytes/macrophages in the bone marrow. In pathological situations, these cells enter the CNS through the perivascular VRS and they differentiate into microglial cells, with a structure and function similar to those of the resident cells (Figure 8) [31, 72]. These cells (resident and invading) also react in a similar manner.

Morphologically, microglia are classified into two basic types, which are now thought to be related to each other: a) small cells with short, branched/ramified processes; and b) round cells without any processes (Figure 6) [8, 9, 84]. In the normal brain, the majority of the microglia are branched cells, while in pathological situations, round cells exist in greater numbers [9]. Indeed, a

transition from resident microglia, usually with processes to activated microglia without processes, has been reported [9, 88, 90]. Plastic and reactive changes in the microglial cells are mostly accompanied by changes in gene expression, allowing the microglial cells to adopt several phenotypes, each with a specific pattern of immunoreactivity or an intracellular store that allows these cells to be differentiated using immunostaining (CD45, CD68, Iba1, LN3, etc.) [9, 78, 85, 86, 88, 90, 92, 93]. Similarly, characterizing the subsets of microglial cells according to both the cytokines/chemokines expressed by them and/or the receptors they carry is a useful way to study the role of microglia.

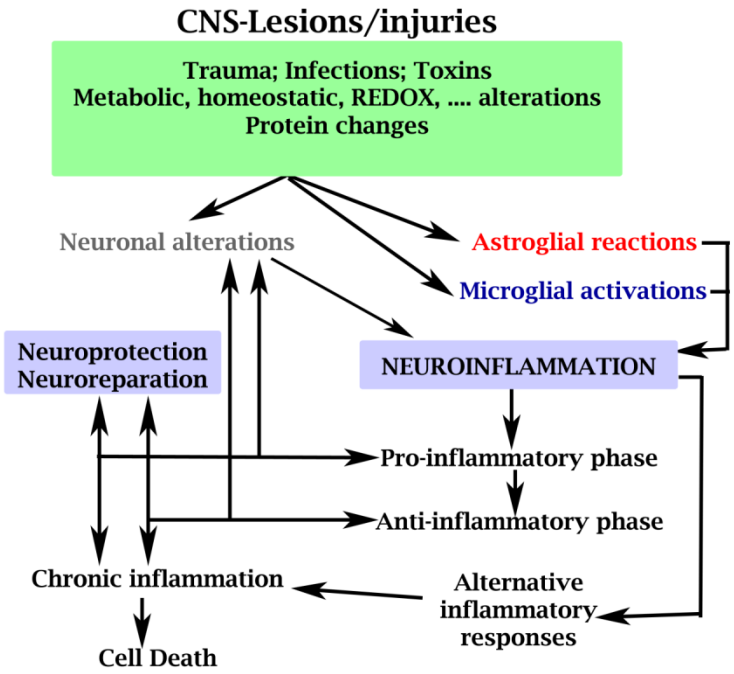

Figure 10 Neuro-inflammation. "Neuro-inflammation" is a specific NS process (or set of processes) based on microgliosis (microglia, here representing the cellular component of the innate immune system in the CNS), although in collaboration with astrogliosis it is closely related to neuronal alterations. In the greatly simplified scheme depicted in the figure, several external or internal insults causing microglia [and astroglial] activation and neuronal alterations are illustrated (injury, trauma, infection, genetic or metabolic alterations, aging, etc.). Pro-inflammatory substances initiate neuro-inflammatory processes, which in turn, incite tissue changes that, in principle, tend to repair the neuronal lesions. In the "classic neuro-inflammatory pathway" (the most frequent response to acute aggressions), a "pro-inflammatory" phase activates defense mechanisms, while an "anti-inflammatory" phase also develops in which the neurons are protected or their damage is repaired. If this neuroprotection/neurorepair fails and chronic inflammation occurs (aging, neurodegeneration), or alternatively, neuro-inflammatory pathways are activated, neuronal aggression could increase, causing the neurons to enter into a degenerative state.

3.2 Microgliosis

Microglial cells exhibit a rapid response to CNS damage and disease, and changes associated with senility have also been observed (Figure 9). The reactivity of resident microglia and the

recruitment of novel microglia is fundamental to neuro-inflammatory response (Figure 6), although astroglia also participate in such events [9, 36]. Del Rio Hortega described the "activation" of microglial cells as a phenomenon closely associated with the phagocytosis of neuronal debris after brain injury [84, 87, 92]. However, the changes occurring in the extracellular matrix (ECM), neurons and glial cells, oxidative stress, and the concentration of secretory products in the local milieu, are all capable of inducing different states of microglial activation [9, 93]. A wide range of pro-inflammatory and anti-inflammatory cytokines and chemokines act on neurons and glial cells, modifying the behavior of neurons and neuronal circuits. Nevertheless, different activation states could result in contrasting effects on the nervous system. Classic microglial activation reflects a pro-inflammatory phase of the innate immune response (IIR) for defending the tissue and destroying the pathogens and the damaged neurons. This microglial activation is associated with the production and release of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukins 1 and 6 (IL–1β and IL–6), and reactive oxygen–nitrogen species (the M1 phenotype). However, in the long term, this reactive process may induce neurotoxicity, inciting a pathological state [84]. Theoretically, classic microglial activation must be rapidly followed by an *"anti-inflammatory phase"* to successfully terminate the IIR at a certain point of time [94-96]. This follow-up phase is associated with the release of anti-inflammatory cytokines that repair the damaged tissue, such as transforming growth factor-β (TGF-β) and interleukins (IL–4, IL–13, and IL–10–the M2 phenotype), and that ultimately promote the shift from the pro-inflammatory phase with the assistance of reactive astrocytes and T cells [95]. Other types of microgliosis or microglial reactivity are *"alternative activation"* and *"acquired deactivation"* [85, 86, 94, 96], both of which are associated with the activation of genes that promote tissue repair and ECM reconstruction. Classic microglial activation is better observed following acute brain injury, while multiple activation states coexist in chronic inflammatory diseases like AD [93]. Whether the different activation states are specific to different subtypes of resting and/or invading microglia expressing only alternative or classic genes remains unknown to date.

Neuropathological studies of different disorders have attempted to define the patterns of microglial infiltration. However, such patterns are difficult to interpret as the morphological and functional characteristics change with each different phase in the evolution of a disease, with each different sub-variety of the same clinical process, as well as from individual to individual [9, 12, 71].

4. Alzheimer's Disease: Therapeutic Strategies Based on Modifying the Activity of Glial Cells

The data obtained from the study of human neurodegenerative diseases and their experimental models highlight the possible therapeutic benefits of using glial cells as targets. A significant proportion of these studies have been conducted in the field of AD, the summary of which is provided in this section. In general, these approaches either stimulated the neuroprotective effects of the neuroglia, or they attempted to arrest or counteract the neurotoxic effects of these cells (Table 1).

Table 1 Some of the most promising studies in gliotherapy within the field of AD have been summarized in this table. Most of them are being carried out after identifying therapeutic targets in astroglia and microglia cells (especially to decrease neuroinflammation). Virtually all of them are in the pre-clinical phase, but many laboratories around the world work to be able to pass them to clinical studies. Many of these possible gliotherapies may be complementary to neurotherapies against AD.

Substance	Study	Effects / Mechanisms	Observations	Ref.
ASTROGLIA				
NGF	Animal models Human patients	Neurotrophic-Neuroprotective	In humans, many attempts to administer NGF (brain injection, intranasal route, virus-based delivery) have failed due to the side-effects produced. New approaches are still being tested	[97-99]
Calcylitics	Cell cultures	Ca^{2+}-antagonists acting on Ca^{2+}-sensing receptors. Decrease the secretion of neurotoxins from astrocytes		[57, 100-104]
Polyamines (putrescine, spermidine)	Cell cultures	Glutamate receptor modulation. Improved glio-neural communication	These substances interact with negatively charged molecules	[68, 105-107]
Reducers of oxidative stress (Curcumin, quercetin, vitamin E, …)	Animal models Human (101)	Neurotrophic-Neuroprotective. Modulate the levels of glutathione	These substances are beneficial to normalize the functions of neurons and to decrease neuro-inflammation due to microgliosis. In humans, they do not seem fully effective (101). Clinical trials are under study	[108, 109]
OLIGODENDROGLIA				
"Senolytic cocktail" (Desatinib –	Cell cultures Animal	Induce death of senescent		[79, 81, 83]

antileukemic- plus Quercetine D + Q - antio)	models	oligodendrocyte progenitor cells. Prevent neurodegeneration		
MICROGLIA				
NSAIDs (colecoxib and flurbiprofen)	Human and experimental models	Decrease the pro-inflammatory reaction of microglia.	No protocol has been approved for human use after clinical trials	[110]
Propentofylline, tannic acid, panfeniacol, etc.	Cells cultures	Decrease the pro-inflammatory reaction of microglia. Inhibition of NF- κ B activation	No protocol has been approved for clinical trials	[111]
Farrerol	Cells cultures Animal models	Decrease the pro-inflammatory reaction of microglia. Decrease the induced upregulation of IL-6, IL-1β and TNF-α, and the induced expression of inducible nitric oxide synthase and cyclooxygenase 2a by enhancing the activation of the Nrf2/Keap1 pathway.	Flavonoid antioxidant and neuroprotective. No protocol has been approved for clinical trials	[112]
Urolithin B	Cells cultures	Decrease the pro-inflammatory reaction of microglia. Inhibits the production of NO and pro-inflammatory cytokines, while it increases that of the anti-inflammatory cytokine IL-10	Metabolite of ellagic acid. Produced in the gut of mammals. No protocol has been approved for clinical trials	[113]
Natural polyphenols	Cells cultures Animal models Human studies	Decrease the pro-inflammatory reaction of microglia. Activation of the nuclear factor Nrf2. Upregulation of heme	No protocol has been approved for human use but human studies are being developing	[114]

		oxygenase-1 mRNA. Increase of NAD(P)H:quinone oxidoreductase 1 activity.		
Exosomes from stem cells	Animal models	Reduce the infiltration of inflammatory cells into the CNS, and decreased demyelination. Increases in the levels of M2 microglia phenotypes and decreased M1 phenotypes	Under study	[115]
Antibodies against pro-inflammatory Cytokines	Animals models	Prevent the pro-inflammatory response of microglia	Under study	[116, 117]
Lipopolysaccharide	Cell cultures Animal model	protect the dopaminergic loss and microglia activation	Under study	[118]
Inhibitors of Protein kinases and phosphodiesterase 4B related to formation of pro-inflammatory cytokines	Cell cultures Animal models	Decrease in pro-inflammatory cytokines	Under study	[119]
Neutral hydroxyl-terminated polyamidoamine (PAMAM)	Cell cultures and animal models	Agent acting on mitochondria of activated microglia	Under study	[120]

4.1 Astroglia

Different strategies may be used to treat/prevent the noxious influence of astrocytes. In particular, approaches involving maintaining neurotrophin production, collaborating with neuronal glutamatergic neurotransmission, and maintaining nervous system homeostasis (Ca^{2+}, K^{+}, etc.) have been followed. Several attempts to administer NGF have failed because of the side-effects produced [96], both when administered using injection and when administered through other highly sophisticated routes (e.g., adeno-associated virus-based delivery [98]). Nonetheless, novel approaches with potential therapeutic benefits (such as the intranasal route [99]) are under investigation.

Amyloid peptides bind specifically to Ca^{2+}-sensing receptors (CaSRs) present on normal astrocytes, leading to the production and secretion of more amyloid and other neurotoxic products (such as NO, vesicular endothelial growth factor, etc.) in AD models. Ca^{2+} antagonists (calcilytics) that decrease the production of neurotoxins have also been reported (57, 100-104]. In the modulation of glutamate receptors, as in the other neuron-glia communication systems, certain polyamines (substances that interact with negatively charged molecules) such as putrescine, spermidine, etc. normalize the glio-neuronal interactions. Biomolecule/polyamine conjugation is considered a promising strategy for the treatment of AD [68, 105-107], sharing the common objective of the possible control of reactive astrogliosis. However, so far, no effective way to control toxic astroglial activation is available. Dampening oxidative stress exerts a significant effect on both neuroprotective and modulatory aspects of astroglial reaction [108]. Indeed, curcumin, quercetin, vitamin E and other substances are capable of modulating the levels of glutathione in neurons and astrocytes [108], although it appears that they do not exhibit their complete effectiveness potential in humans [109].

4.2 Oligodendroglia

Prevention of cell senescence and/or the elimination of senescent $NG2^{+}$ cells represent potential preventive therapeutic strategies for the treatment of AD and other neurodegenerative diseases [79, 81, 83]. A senolytic combination of dasatinib and quercetin (D + Q) has been reported to cause the death of senescentoligodendrocyte precursors OPCs induced by Aβ *in vitro* [79].

4.3 Microglia

Inhibition of neuro-inflammatory response forms the basis of the approaches followed to prevent neurodegenerative diseases or to terminate their progression. In the course of aging and neurodegenerative pathologies, changes occur in the morphology and functional phenotypes of the different sets of microglial cells (both resident and invasive microglia). In general, the M1 phenotype is considered to be responsible for neuro-inflammation, with these microglial cells secreting pro-inflammatory cytokines/chemokines like TNF-α, IL12, etc., while the M2 phenotype of reactive inflammatory cells is associated with the secretion of anti-inflammatory cytokines/chemokines such as IL–10, TGF-β, etc. In different pathologies, there is an imbalance between these two phenotypes in distinct phases of the pathogenesis, as well as in different regions of the brain and different areas of each of the affected regions. Several of these variations remain poorly understood, although it is a general supposition that the shift from M1 to M2 phenotype is beneficial in most processes, irrespective of the phase of the disease or the areas affected [121].

Various therapeutic strategies focusing on microglia have been evaluated so far. The microglial response is governed by extracellular factors in the nervous tissue and by alterations to neurons, which must be detected and corrected as soon as possible [122]. External environmental factors, diet, metabolic alterations (such as obesity and insulin resistance), cardiovascular processes, toxic drugs, etc. may incite or accentuate inflammatory phenomena that ultimately lead to AD and other neurodegenerative diseases [9, 85, 123-125]. Therefore, addressing AD risks and inflammatory phenomena should be considered among the initial measures to be undertaken in

AD treatment [122-125]. For instance, hypercaloric diets appear to induce microgliosis in experimental AD models [123].

The best-studied substances for AD treatment are anti-inflammatory agents, both in humans and in experimental models. NSAIDs (non-steroidal anti-inflammatory drugs) such as colecoxib and flurbiprofen have been tested in humans and experimental models of AD with conflicting results. Cyclo-oxygenase 2 (COX–2) produces inflammation in several tissues, including the CNS [110], while it is also activated by cholinergic receptors on neurons and astrocytes via signaling pathways that are not involved in the inflammatory phenomena [110]. Therefore, COX–2 activation cannot be exclusively considered a neurodegenerative microglial response, rather it should be considered a component of a global adaptive response in certain neuroprotective/reparative phases when CNS alterations occur [110]. Other anti-inflammatory compounds that decrease the pro-inflammatory reaction of microglia have also been tested, such as propentofylline, tannic acid and panpheniacol [111-114], although no protocols for their administration are available currently.

In recent years, it has been demonstrated that exosomes released by stem cells are capable of attenuating inflammation and demyelination in the CNS of several neurodegenerative disease models [115]. Exosome treatment may produce a significant increase in anti-inflammatory cytokines (e.g., IL–10 and TGF-β) and a decrease in pro-inflammatory mediators (e.g., TNF-α and IL–12). Similarly, both mesenchymal stem cells [116] and adipose-derived stem cells [118] may control or prevent microglial pro-inflammatory reactions.

Protein kinases [119] and phosphodiesterase 4B [126, 127] are closely associated with the production of pro-inflammatory cytokines by reactive microglia after induction by amyloid peptides and other toxic substances. Therefore, they may represent interesting therapeutic targets. A wide range of approaches to dampen oxidative stress closely related to the neuro-inflammatory reaction of microglia have been proposed (diets, healthy lifestyles and antioxidants) [125]. The proposed therapeutic approaches may be simple or complex. N-acetyl cysteine is used widely, although it provides limited benefits in human therapy. Studies concerning monocarriers of antioxidants that act on the mitochondria of activated microglia in neurodegenerative diseases, such as neutral hydroxyl-terminated polyamidoamine (PAMAM) dendrimers, appear to exert a level of control on pro-inflammatory microglial reactions [120]. It may also be possible to use antibodies that block pro-inflammatory substances [117].

5. Conclusions

Neurons are often accompanied by neuroglial cells, which cooperate with the former in all their activities. The study of neuroglial cells has remained undervalued for years; nonetheless, the demonstration that these cells are required for the proper functioning of neurons has brought these cells to the forefront of scientific concern. Different families of glia exist, namely, astroglia, oligodendroglia (including the $NG2^+$ subtypes) and microglia. Plastic changes to these glial cells parallel the plasticity of neurons, which optimizes the activity of the neuronal circuits. A reactive status (“gliosis”) may be adopted by different cell types/subtypes within the three families of glia, in which not only the morphology and the phenotype is modified, rather new activities are undertaken as well, particularly in pathological conditions and in association with the aging of the CNS. All glial cells are involved in global neuroprotection, as well as in neurodegenerative phenomena. Profound changes occur to glia during the physiological aging of the brain, in AD and

in neurodegenerative disorders. Indeed, several of these changes are supposed to be of a neurodegenerative nature, although gliosis certainly fulfills a neuroprotective role in certain situations. The biggest challenge now is to differentiate which of these glial changes are beneficial to the brain and which ones are harmful.

Enhancing knowledge regarding the roles of neuroglial cells (astroglia, oligodendroglia, and microglia) and their neuroprotective and neurodegenerative reactions in aging, AD, and other neurodegenerative diseases, would increase the possibilities of designing novel therapeutic strategies for these conditions. The qualitative and quantitative study of the region-specific alterations occurring in microglial subtypes in aging and AD (defining gene sets in specific astroglia and microglia within each region and in each pathological situation) could provide novel insights into the disease, as well as novel therapeutic possibilities [128]. Currently, there is no clarity regarding how to develop effective therapies (either preventive or regulating the progression of the diseases), although several preclinical studies are in progress. Therefore, different sets of neuroglial cells are probably going to be defined as effective therapeutic targets. Toxic proteins (amyloid) and other factors (cytokines, chemokines, etc.) work together in the initiation and progression of AD or other neurodegenerative diseases, while at the same time, cellular mechanisms (neuronal and glial) to counteract them are initiated. Consequently, in order to achieve the objective of controlling CNS degeneration, the therapeutic strategies adopted should act simultaneously on neurodegeneration and neuroprotection [9].

Author Contributions

All the authors contribute likewise in the organization and writing of the review, based on the results of their studies and the analysis of the bibliography Specify each author's contribution to this work respectively.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Virchow R. Die Cellularpathologie in ihrer Begrundung auf physiologische und pathologische Gewebelehre. Berlin: Verlag; 1858.
2. Ramón y Cajal S. Contribution a la connaissance de la nevroglie cerebrale et cerebelleuse dans la paralysie generale progressive. Trav Lab Recher Biol Univ Madrid. 1925; 23: 157-216.
3. Penfield W. Neuroglia: Normal and pathological. In: Penfield W, Ed. Cytology and cellular pathology of the nervous system. Vol II. New York: PB Hoeberr Inc; 1932. p. 423-479.
4. Ramón y Cajal S. Histologie du systeme nerveux de l´homme et des vertebres (translated by L. Azoulay), vols I and II. Paris: Maloine; 1909-1911. (Reprinted 1952 and 1955. Madrid: Consejo Superior de Investigaciones Científicas)
5. Ramón y Cajal S. Contribución al conocimiento de la neuroglia del cerebro humano. Trab Lab Invest Biol. 1913; 11: 255-315.
6. Retzius G. Die Neuroglia des Gehirns beim Menschen und bei Saugethieren: Die Neuroglia des Kleinhirns. Biologische Untersuchungen. Neue Folge. 1894; 4: 16-20.

7. Terrazas R. Notas sobre la neuroglia del cerebelo y el crecimiento de los elementos nerviosos. Rev Trim Micrograf. 1897; 2: 49-65.
8. Del Rio Hortega P. El “tercer elemento” de los centros nerviosos. Poder fagocitario y movilidad de la microglia. Bol Soc Esp Biol. 1919; 8: 68-82.
9. Toledano A, Alvarez MI, Toledano-Diaz A, Merino JJ, Rodriguez JJ. Brain local and regional neuroglial alterations in Alzheimer´s disease: Cell types, responses and implications. Curr Alzheimer Res. 2016; 13: 321-344.
10. Toledano A, Merino JJ, Rodríguez JJ. Neuroglia in Alzheimer`s disease: From cohort to contestant in the disease progression and its therapy. Curr Alzheimer Res. 2016; 13.
11. Del Rio Hortega P. La glia de escasas radiaciones (oligodendroglia). Bol Real Soc Esp Hist Nat. 1921; 21: 63-92.
12. Alvarez MI, Rivas L, Lacruz C, Toledano A. Astroglial cell subtypes in the cerebella of normal adults, elderly adults, and patients with Alzheimer's disease: A histological and immunohistochemical comparison. Glia. 2015; 62: 287-312.
13. Schools GP, Zhou M, Kimelberg HK. Electrophysiologically "complex" glial cells freshly isolated from the hippocampus are immunopositive for the chondroitin sulfate proteoglycan NG2. J Neurosci Res. 2003; 73: 765-777.
14. Levine JM, Card JP. Light and electron microscopic localization of a cell surface antigen (NG2) in the rat cerebellum: Association with smooth protoplasmic astrocytes. J Neurosci. 1987; 7: 2711-2720.
15. Crawford AH, Stockley JH, Tripathi RB, Richardson WD, Franklin RJ. Oligodendrocyte progenitors: Adult stem cells of the central nervous system? Exp Neurol. 2014; 260: 50-55.
16. Rivera A, Vanzuli I, Rodríguez JJ, Butt A. Decreased regenerative capacity of oligodendrocyte progenitor cells (NG2-Glia) in the ageing brain: A vicious cycle of synaptic dysfunction, myelin loss and neuronal disruption?. Curr Alzheimer Res. 2016; 13, 413-418.
17. Bankston AN, Mandler MD, Feng Y. Oligodendroglia and neurotrophic factors in neurodegeneration. Neurosci Bull. 2013; 29: 216-228.
18. Vernadakis A. Glia-neuron intercommunications and synaptic plasticity. Prog Neurobiol. 1996; 49: 185-214.
19. Nedergaard M, Ransom B, Goldman SA. New roles for astrocytes: Redefining the functional architecture of the brain. Trends Neurosci. 2003; 26: 523-530.
20. Parpura V, Heneka MT, Montana V, Oliet SH, Schousboe A, Haydon PG, et al. Glial cells in (patho)physiology. J Neurochem. 2012; 121: 4-27.
21. Salter MW, Beggs S. Sublime microglia: Expanding roles for the guardians of the CNS. Cell. 2014; 158: 15-24.
22. Tremblay ME, Stevens B, Sierra A, Wake H, Bessis A, Nimmerjahn A. The role of microglia in the healthy brain. J Neurosci. 2011; 31: 16064-16069.
23. Morris GP, Clark IA, Zinn R, Vissel B. Microglia: A new frontier for synaptic plasticity, learning and memory, and neurodegenerative disease research. Neurobiol Learn Mem. 2013; 105: 40-53.
24. Ota Y, Zanetti AT, Hallock RM. The role of astrocytes in the regulation of synaptic plasticity and memory formation. Neural Plast. 2013; 2013: 185463.

25. Xavier AL, Menezes JR, Goldman SA, Nedergaard M. Fine-tuning the central nervous system: Microglial modelling of cells and synapses. Philos Trans R Soc Lond B Biol Sci. 2014; 369: 20130593.
26. Araque A, Carmignoto G, Haydon PG, Oliet SH, Robitaille R, Volterra A. Gliotransmitters travel in time and space. Neuron. 2014; 81: 728-739.
27. Stuchlik A. Dynamic learning and memory, synaptic plasticity and neurogenesis: An update. Front Behav Neurosci. 2014; 8: 106.
28. Viola GG, Rodrigues L, Americo JC, Hansel G, Vargas RS, Biasibetti R, et al. Morphological changes in hippocampal astrocytes induced by environmental enrichment in mice. Brain Res. 2009; 1274: 47- 54.
29. Perez-Alvarez A, Navarrete M, Covelo A, Martin ED, Araque A. Structural and functional plasticity of astrocyte processes and dendritic spine interactions. J Neurosci. 2014; 34: 12738-12744.
30. Rodriguez JJ, Olabarria M, Chvatal A, Verkhratsky A. Astroglia in dementia and Alzheimer's disease. Cell Death Differ. 2009; 16: 378-385.
31. Mosher KI, Wyss-Coray T. Microglial dysfunction in brain aging and Alzheimer's disease. Biochem Pharmacol. 2014; 88: 594-604.
32. Nagelhus EA, Amiry-Moghaddam M, Bergersen LH, Bjaalie JG, Eriksson J, Gundersen V, et al. The glia doctrine: Addressing the role of glial cells in healthy brain ageing. Mech Ageing Dev. 2013; 134: 449-459.
33. Benarroch EE. Microglia: Multiple roles in surveillance, circuit shaping, and response to injury. Neurology. 2013; 81: 1079-1088.
34. Papa M, De Luca C, Petta F, Alberghina L, Cirillo G. Astrocyteneuron interplay in maladaptive plasticity. Neurosci Biobehav Rev. 2014; 42: 35-54.
35. Toledano A, Álvarez MI, Toledano-Díaz A. Nuevos conceptos sobre la funcionalidad del sistema nervioso: La revolución de las células gliales. I. Las relaciones neuro-gliales. An Real Acad Farm. 2015; 81: 11-18.
36. Agnati LF, Cortelli P, Pettersson R, Fuxe K. The concept of trophic units in the central nervous system. Prog Neurobiol. 1995; 46: 561-574.
37. Lecrux C, Hamel E. The neurovascular unit in brain function and disease. Acta Physiol. 2011; 203: 47-59.
38. Verkhratsky A, Nedergaard M, Hertz L. Why are astrocytes important? Neurochem Res. 2015; 40: 389-401.
39. Yang Y, Vidensky S, Jin L, Jie C, Lorenzini I, Frank M, et al. Molecular comparison of GLT1+ and ALDH1L1+ astrocytes *in vivo* in astroglial reporter mice. Glia. 2011; 59: 200-207.
40. Kulijewicz-Nawrot M, Sykova E, Chvatal A, Verkhratsky A, Rodriguez JJ. Astrocytes and glutamate homoeostasis in Alzheimer's disease: A decrease in glutamine synthetase, but not in glutamate transporter-1, in the prefrontal cortex. ASN Neuro. 2013; 5: 273-282.
41. Verkhratsky A, Olabarria M, Noristani HN, Yeh CY, Rodriguez JJ. Astrocytes in Alzheimer's disease. Neurotherapeutics. 2010; 7: 399-412.
42. Verkhratsky A, Rodriguez JJ, Parpura V. Astroglia in neurological diseases. Future Neurol. 2013; 8: 149-158.
43. Verkhratsky A, Nedergaard M. Astroglial cradle in the life of the synapse. Philos Trans R Soc Lond B Biol Sci. 2014; 369: 20130595.

44. Oberheim NA, Takano T, Han X, He W, Lin JH, Wang F, et al. Uniquely hominid features of adult human astrocytes. J Neurosci. 2009; 29: 3276-3287.
45. Bushong EA, Martone ME, Jones YZ, Ellisman MH. Protoplasmic astrocytes in CA1 stratum radiatum occupy separate anatomical domains. J Neurosci. 2002; 22: 183-192.
46. Halassa MM, Fellin T, Takano H, Dong JH, Haydon PG. Synaptic islands defined by the territory of a single astrocyte. J Neurosci. 2007; 27: 6473-6477.
47. Reichenbach A, Derouiche A, Kirchhoff F. Morphology and dynamics of perisynaptic glia. Brain Res Rev. 2010; 63: 11-25.
48. Allaman I, Belanger M, Magistretti PJ. Astrocyte-neuron metabolic relationships: for better and for worse. Trends Neurosci. 2011; 34: 76-87.
49. Oberheim NA, Goldman SA, Nedergaard M. Heterogeneity of astrocytic form and function. Meth Mol Biol. 2012; 814: 23-45.
50. Mitew S, Kirkcaldie MT, Dickson TC, Vickers JC. Altered synapses and gliotransmission in Alzheimer's disease and AD model mice. Neurobiol Aging. 2013; 34: 2341-2351.
51. Lim D, Ronco V, Grolla AA, Verkhratsky A, Genazzani AA. Glial calcium signalling in Alzheimer's disease. Rev Physiol Biochem Pharmacol. 2014; 167: 45-65.
52. Nedergaard M, Verkhratsky A. Artifact versus reality--how astrocytes contribute to synaptic events. Glia. 2012; 60: 1013-1023.
53. Tsai HH, Li H, Fuentealba LC, Molofsky AV, Taveira-Marques R, Zhuang H, et al. Regional astrocyte allocation regulates CNS synaptogenesis and repair. Science. 2012; 337: 358-362.
54. Sahlender DA, Savtchouk I, Volterra A. What do we know about gliotransmitter release from astrocytes? Philos Trans R Soc Lond B Biol Sci. 2014; 369: 20130592.
55. Carmona P, Molina M, Toledano A. Blood-based biomarkers of Alzheimer´s disease: Diagnostic algorithms and new technologies. Curr Alzheimer Res. 2016; 13, 450-464.
56. Iliff JJ, Nedergaard M. Is there a cerebral lymphatic system? Stroke. 2013; 44: S93-S95.
57. Dal Pra I, Chiarini A, Pacchiana R, Gardenal E, Chakravarthy B, Whitfield JF, et al. Calcium-sensing receptors of human astrocyteneuron teams: Amyloid-β-driven mediators and therapeutic targets of Alzheimer's disease. Curr Neuropharmacol. 2014; 12: 353-364.
58. Faghih MM, Sharp MK. Is bulk flow plausible in perivascular, paravascular and paravenous channels? Fluids Barriers CNS. 2018; 15: 17.
59. Plog BA, Nedergaard M. The glymphatic system in central nervous system health and disease: Past, present, and future. Annu Rev Pathol. 2018; 13: 379-394.
60. Albargothy NJ, Johnston DA, MacGregor-Sharp M, Weller RO, Verma A, Hawkes CA, et al. Convective influx/glymphatic system: Tracers injected into the CSF enter and leave the brain along separate periarterial basement membrane pathways. Acta Neuropathol. 2018; 136: 139-152.
61. Owens T, Bechmann I, Engelhardt B. Perivascular spaces and the two steps to neuroinflammation. J Neuropathol Exp Neurol. 2008; 67: 1113-1121.
62. Teo L, Bourne JA. Current opinion on a role of the astrocytes in neuroprotection. Neural Regen Res. 2018; 13: 797-798.
63. Monzón-Mayor M, Alvarez M, Arbelo-Galvan J, Romero-Aleman M, Yanes C, Plaza ML, et al. Long-term evolution of local, proximal and remote astrocyte responses after diverse nucleus basalis lesioning (an experimental Alzheimer model): GFAP immunocytochemical study. Brain Res. 2000; 865: 245-258.

64. Achucarro N, Gayarre M. Contribucion al estudio de la neuroglia en la corteza de la demencia senil y su participacion en la alteración celular de Alzheimer. Trab Lab Invest Biol Univ Madrid. 1914; 12: 68-83.
65. Achúcarro N, Gayarre M. La corteza cerebral en la demencia paralitica con el nuevo método del oro y sublimado de Cajal. Trab Lab Invest Biol Univ Madrid. 1914; 12: 1-38.
66. Kamphuis W, Kooijman L, Orre M, Stassen O, Pekny M, Hol EM. GFAP and vimentin eficiency alters gene expression in astrocytes and microglia in wild-type mice and changes the transcriptional response of reactive glia in mouse model for Alzheimer's disease. Glia. 2015; 63: 1036-1056.
67. Mathur R, Ince PG, Minett T, Garwood CJ, Shaw PJ, Matthews FE, et al. A reduced astrocyte response to β-amyloid plaques in the ageing brain associates with cognitive impairment. PLoS One. 2015; 10: e0118463.
68. Nirzhor SSR, Khan RI, Neelotpol S. The biology of glial cells and their complex roles in Alzheimer's disease: New opportunities in therapy. Biomolecules. 2018; 10 E93.
69. Suarez I, Bodega G, Arilla E, Felipo V, Fernandez B. The expression of nNOS, iNOS and nitrotyrosine is increased in the rat cerebral cortex in experimental hepatic encephalopathy. Neuropathol Appl Neurobiol. 2006; 32: 594-604.
70. Rodriguez JJ, Yeh CY, Terzieva S, Olabarria M, Kulijewicz- Nawrot M, Verkhratsky A. Complex and region-specific changes in astroglial markers in the aging brain. Neurobiol Aging. 2014; 5: 15-23.
71. Berciano MT, Andres MA, Calle E, Lafarga M. Age-induced hypertrophy of astrocytes in rat supraoptic nucleus: A cytological, morphometric, and immunocytochemical study. Anat Rec. 1995; 243: 129-144.
72. Ramón y Cajal, S. Degeneration and regeneration of the nervous system. New York: Harper Press; 1969.
73. Furusho M, Roulois AJ, Franklin RJ, Bansal R. Fibroblast growth factor signaling in oligodendrocyte-lineage cells facilitates recovery of chronically demyelinated lesions but is redundant in acute lesions. Glia. 2015; 63: 1714-1728.
74. Lye JJ, Latorre E, Lee BP, Bandinelli S, Holley JE, Gutowski NJ, et al. Astrocyte senescence may drive alterations in GFAPalpha, CDKN2A p14 (ARF), and TAU3 transcript expression and contribute to cognitive decline. Geroscience. 2019; 41: 561-573.
75. Tamas Csipo T, Lipecz A, Ashpole NM, Balasubramanian P, Tarantini S. Astrocyte senescence contributes to cognitive decline. GeroScience 2020; 42: 51-55.
76. Benarroch EE. Oligodendrocytes: Susceptibility to injury and involvement in neurologic disease. Neurology. 2009; 72: 1779-1785.
77. Kipp M, Victor M, Martino G, Franklin RJ. Endogeneous remyelination: Findings in human studies. CNS Neurol Disord Drug Targets. 2012; 11: 598-609.
78. Miron VE, Boyd A, Zhao JW, Yuen TJ, Ruckh JM, Shadrach JL, et al. M2 microglia and macrophages drive oligodendrocyte differentiation during CNS remyelination. Nat Neurosci. 2013; 16: 1211-1218.
79. Zhang P, Yuki Kishimoto Y, Grammatikakis I, Gottimukkala K, Cutler RG, Zhang S, et al. Senolytic therapy alleviates Aβ-associated oligodendrocyte progenitor cell senescence and cognitive deficits in an Alzheimer's disease model. Nat Neurosci. 2019; 22: 719-728.

80. Childs BG, Durik M, Baker DJ, van Deursen JM. Cellular senescence in aging and age-related disease: From mechanisms to therapy. Nat Med 2015; 21: 1424-1435.
81. Nicaise AM, Wagstaff LJ, Willis CM, Paisie C, Chandok H, Robson P, et al. Cellular senescence in progenitor cells contributes to diminished remyelination potential in progressive multiple sclerosis. Proc Natl Acad Sci U S A. 2019; 116: 9030-9039.
82. Zhu Y, Armstrong JL, Tchkonia T, Kirkland JL. Cellular senescence and the senescent secretory phenotype in age-related chronic diseases. Curr Opin Clin Nutr Metab Care. 2014; 17: 324-328.
83. Holtzman D, Ulrich J. Senescent glia spell trouble in Alzheimer's disease. Nat Neurosci. 2019; 22: 681-690.
84. Del Rio Hortega P. Histogenesis y evolucion normal, exodo y distribucion regional de la microglia. Mem Real Soci Esp Hist Nat. 1921; 11: 213-268.
85. Navarro V, Sanchez-Mejias E, Jimenez S, Muñoz-Castro C, Sanchez-Varo R, Davila JC, et al. Microglia in Alzheimer's disease: Activated, dysfunctional or degenerative. Front Aging Neurosci. 2018; 10: 140.
86. Guedes JR, Lao T, Cardoso AL, El Khoury J. Roles of microglial and monocyte chemokines and their receptors in regulating Alzheimer's disease-associated amyloid-β and tau pathologies. Front Neurol. 2018; 9: 549.
87. Wyss-Coray T, Rogers J. Inflammation in Alzheimer disease-a brief review of the basic science and clinical literature. Cold Spring Harb Perspect Med. 2012; 2: a006346.
88. Meraz-Rios MA, Toral-Rios D, Franco-Bocanegra D, Villeda- Hernandez J, Campos-Pena V. Inflammatory process in Alzheimer's Disease. Front Integr Neurosci. 2013; 7: 59.
89. Perez-Nievas BG, Serrano-Pozo A. Deciphering the astrocyte reaction in Alzheimer's disease. Front Aging Neurosci. 2018; 10: 114.
90. Prinz M, Priller J, Sisodia SS, Ransohoff RM. Heterogeneity of CNS myeloid cells and their roles in neurodegeneration. Nat Neurosci. 2011; 14: 1227-1235.
91. Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science. 2005; 308: 1314-1318.
92. Del Rio-Hortega P. Microglia. In: Cytology and cellular pathology of the nervous system, Vol. II. (Ed: Penfield W). New York: Hafner; 1932. p. 483-534.
93. Colton C, Wilcock DM. Assessing activation states in microglia. CNS Neurol Disord Drug Targets. 2010; 9: 174-191.
94. Han J, Ulevitch RJ. Limiting inflammatory responses during activation of innate immunity. Nat Immunol. 2005; 6: 1198-1205.
95. Colton CA. Heterogeneity of microglial activation in the innate immune response in the brain. J Neuroimmune Pharmacol. 2009; 4: 399- 418.
96. Chhor V, Le Charpentier T, Lebon S, Ore MV, Celador IL, Josserand J, et al. Characterization of phenotype markers and neuronotoxic potential of polarised primary microglia in vitro. Brain Behav Immun. 2013; 32: 70-85.
97. Tuszynski MH, Thal L, Pay M, Salmon DP, U HS, Bakay R, et al. A phase 1clinical trial of nerve growth factor gene therapy for Alzheimer disease. Nat Med. 2005; 11: 551-555.
98. Mandel RJ. CERE-110, an adeno-associated virus-based gene delivery vector expressing human nerve growth factor for the treatment of Alzheimer'sdisease. Curr Opin Mol Ther. 2010; 12: 240-247.

99. Capsoni S, Marinelli S, Ceci M, Vignone D, Amato G, Malerba F, et al. Intranasal ‘‘painless’’ human nerve growth factors slows amyloid neurodegenerationand prevents memory deficits in App X PS1 mice. PLoS One. 2012; 7: e37555.
100. Chiarini A, Dal Pra I, Menapace L, Pacchiana R, Whitfield JF, Armato U. Soluble amyloid beta-peptide and myelin basic protein strongly stimulate, alone and in synergism with combined proinflammatory cytokines, the expression of functional nitric oxide synthase-2 in normal adult human astrocytes. Int J Mol Med. 2008; 16: 801-807.
101. Chiarini A, Gardenal E, Whitfield JF, Chakravarthy B, Armato U, Dal Pra I. Preventing the spread of Alzheimer's disease neuropathology: A role for calcilytics? Curr Pharm Biotechnol. 2015; 16: 696-706.
102. Chiarini A, Dal Pra I, Marconi M, Chakravarthy B, Whitfield JF, Armato U. Calcium-sensing receptor (CaSR) in human brain's pathophysiology: Roles in late-onset Alzheimer's disease (LOAD). Curr Pharm Biotechnol. 2009; 10: 317-326.
103. Dal Pra I, Chiarini A, Pacchiana R, Gardenal E, Chakravarthy B, Whitfield JF, et al. Calcium-sensing receptors of human as astrocyte-neuron teams: Amyloid-β-driven mediators and therapeutic targets of Alzheimer's disease. Curr Neuropharmacol. 2014; 12: 353-364.
104. Chiarini A, Armato U, Liu D, DalPrà I. Calcium-sensing receptors of human neural cells play crucial roles in Alzheimer’s disease. Front Physiol. 2016; 7: 134.
105. Pihlaja R, Koistinaho J, Kauppinen R, Sandholm J, Tanila H, Koistinaho M. Multiple cellular and molecular mechanisms Are involved in human Aβ clearance by transplanted adult astrocytes. Glia. 2011; 59: 1643-1657.
106. Skatchkov SN, Woodbury-Fariña MA, Eaton M. The role of glia in stress: Polyamines and brain disorders. Psychiatr Clin North Am. 2014; 37: 653-678.
107. Guerra GP, Rubin MA, Mello CF. Modulation of learning and memory by natural polyamines. Pharmacol Res. 2016; 112: 99-118.
108. Lavoie S, Chen Y, Dalton TP, Gysin R, Cuénod M, Steullet P, et al. Curcumin, quercetin, and tBHQ modulate glutathione levels in astrocytes and neurons: Importance of the glutamate cysteine ligase modifier subunit. J Neurochem. 2009; 108: 1410-1422.
109. Fritsche S, Wang X, Jung C. Recent advances in our understanding of tocopherol biosynthesis in plants: An overview of key genes, functions, and breeding of vitamin E improved crops. Antioxidants. 2017; 6: 99.
110. Toledano A, Alvarez MI, Toledano-Diaz A. Diversity and variability of the nicotine effects on different brain cortical regions. Therapeutic and toxicologic implications. Central Nervous Syst Agents Med Chem. 2010; 10: 180-206.
111. Wu Y, Zhong L, Yu Z, Qi J. Anti-neuroinflammatory effects of tannic acid against lipopolysaccharide-induced BV2 microglial cells via inhibition of NF-κB activation. Drug Dev Res. 2019; 80: 262-268.
112. Cui B, Guo X, You Y, Fu R. Farrerol attenuates MPP+ -induced inflammatory response by TLR4 signaling in a microglia cell line. Phytother Res. 2019; 33: 1134-1141.
113. Lee G, Park JS, Lee EJ, Ahn JH, Kim HS. Anti-inflammatory and antioxidant mechanisms of urolithin B in activated microglia. Phytomedicine. 2018; 55: 50-57.
114. Mattioli R, Francioso A, d’Erme M, Trovato M, Mancini P, Piacentini L, et al. Anti-inflammatory activity of a polyphenolic extract from arabidopsis thaliana in in vitro and in vivo models of Alzheimer’s disease. Int J Mol Sci. 2019; 20: E708.

115. Li Z, Liu F, He X, Yang X, Shan F, Feng J. Exosomes derived from mesenchymal stem cells attenuate inflammation and demyelination of the central nervous system in EAE rats by regulating the polarization of microglia. Int Immunopharmacol. 2019; 67: 268-280.
116. Kim SH, Oh KW, Jin HK, Bae JS. Immune inflammatory modulation as a potential therapeutic strategy of stem cell therapy for ALS and neurodegenerative diseases. BMB Rep. 2018; 51: 545-546.
117. Wang S, Colonna M. Microglia in Alzheimer's disease: A target for immunotherapy. J Leukoc Biol. 2019; 106: 219-227.
118. Muñoz MF, Argüelles S, Medina R, Cano M, Ayala A. Adipose-derived stem cells decreased microglia activation and protected dopaminergic loss in rat lipopolysaccharide model. J Cell Physiol. 2019; 234: 13762-13772.
119. Lee SH, Suk K. Kinase-based taming of brain microglia toward disease-modifying therapy. Front Cell Neurosci. 2018, 12: 474.
120. Sharma A, Liaw K, Sharma R, Zhang Z, Kannan S, Kannan RM. Targeting mitochondrial dysfunction and oxidative stress in activated microglia using dendrimer-based therapeutics. Theranostics. 2018, 8: 5529-5547.
121. Ahmad MH, Fatima M, Mondal AC. Influence of microglia and astrocyte activation in the neuroinflammatory pathogenesis of Alzheimer's disease: Rational insights for the therapeutic approaches. J Clin Neurosci. 2019; 59: 6-11.
122. Katsumoto A, Takeuchi H, Takahashi K, Tanaka F. Microglia in Alzheimer's disease: Risk factors and inflammation. Front Neurol. 2018; 9: 978.
123. Toledano-Díaz A, Alvarez MI, Toledano A. Reproduction and brain. I morphofunctional basis of brain control: Advances and therapeutical implications. Anales de la Real Academia Nacional de Farmacia. 2017; 83. 224-240.
124. Yeh H, Ikezu T. Transcriptional and epigenetic regulation of microglia in health and disease. Trends Mol Med. 2019; 25: 96-111.
125. Rodríguez-Casado A, Toledano-Díaz A, Toledano A. Defective insulin signalling, mediated by inflammation, connects obesity to Alzheimer disease; relevant pharmacological therapies and preventive dietary interventions. Curr Alzheimer Res. 2017; 14: 894-911.
126. Smith DL, Pozueta J, Gong B, Arancio O, Shelanski M. Reversal of long-term dendritic spine alterations in Alzheimer disease models. Proc Natl Acad Sci U S A. 2009; 106: 16877-16882.
127. Gurney ME, D'Amato EC, Burgin AB. Phosphodiesterase-4 (PDE4) molecular pharmacology and Alzheimer's disease. Neurotherapeutics. 2015; 12: 49-56.
128. Patir A, Shih B, McColl BW, Freeman TC. A core transcriptional signature of human microglia: Derivation and utility in describing region-dependent alterations associated with Alzheimer's disease. Glia. 2019; 67: 1240-1253.

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