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Glial Asthenia and Functional Paralysis: A New Perspective on Neurodegeneration and Alzheimer's Disease

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Abstract

Neuroglia are represented by several population of cells heterogeneous in structure and function that provide for the homeostasis of the brain and the spinal cord. Neuroglial cells are also central for neuroprotection and defence of the central nervous system against exo- and endogenous insults. At the early stages of neurodegenerative diseases including Alzheimer's disease neuroglial cells become asthenic and lose some of their homeostatic, neuroprotective, and defensive capabilities. Astroglial reactivity, for example, correlates with preservation of cognitive function in patients with mild cognitive impairment and prodromal Alzheimer's disease. Here, we overview the experimental data indicating glial paralysis in neurodegeneration and argue that loss of glial function is fundamental for defining the progression of neurodegenerative diseases.

Keywords

neuroglia, astrocyte, oligodendrocyte, microglia, neurodegeneration, Alzheimer's disease, reactive astrogliosis

Multicellular Nature of Neuropathology

Omnis cellula e cellula, the concept introduced by Rudolf Virchow[1] remains the fundamental principle of physiology and pathophysiology, which regards the dissection of cellular mechanisms as a main step in understanding and revealing the nature of the normal function and of the disease. The cellular pathophysiology therefore reduces morbid developments from the whole body to the behavior of individual cell types or even individual cells. In conforming to this principle, experimental neurology is the most extreme case, because it considers neurological disorders solely (or almost solely) from neuronocentric angle.

This neuronocentricity comes at odds with the intricate structure of the neural tissue formed by many types of cells of different origin, physiology, and functional specialization. These many cellular types exist in a state of continuous communication, which defines the functional outputs of the nervous system; similarly these heterogeneous cell populations and their interrelations represent the substrate for pathology.

The cells dwelling in the central nervous system (CNS) are broadly classified (according to their developmental roots) into cells of ectodermal and mesodermal origin (Fig. 1). The ectoderm derived cells are neural cells (the scions of neuroepithelial common progenitor) represented by neurones, astroglia, oligodendroglia, and NG2 glia. The mesodermal cells are subdivided into CNS resident microglia, and cellular elements of blood vessels such as endothelial cells, pericytes, smooth muscle cells and fibroblasts. In pathological conditions the CNS parenchyma can also be invaded by blood cells such as platelets, leukocytes and various macrophages. In summary, each and every cell composing CNS tissue is responsible for the physiological function and is

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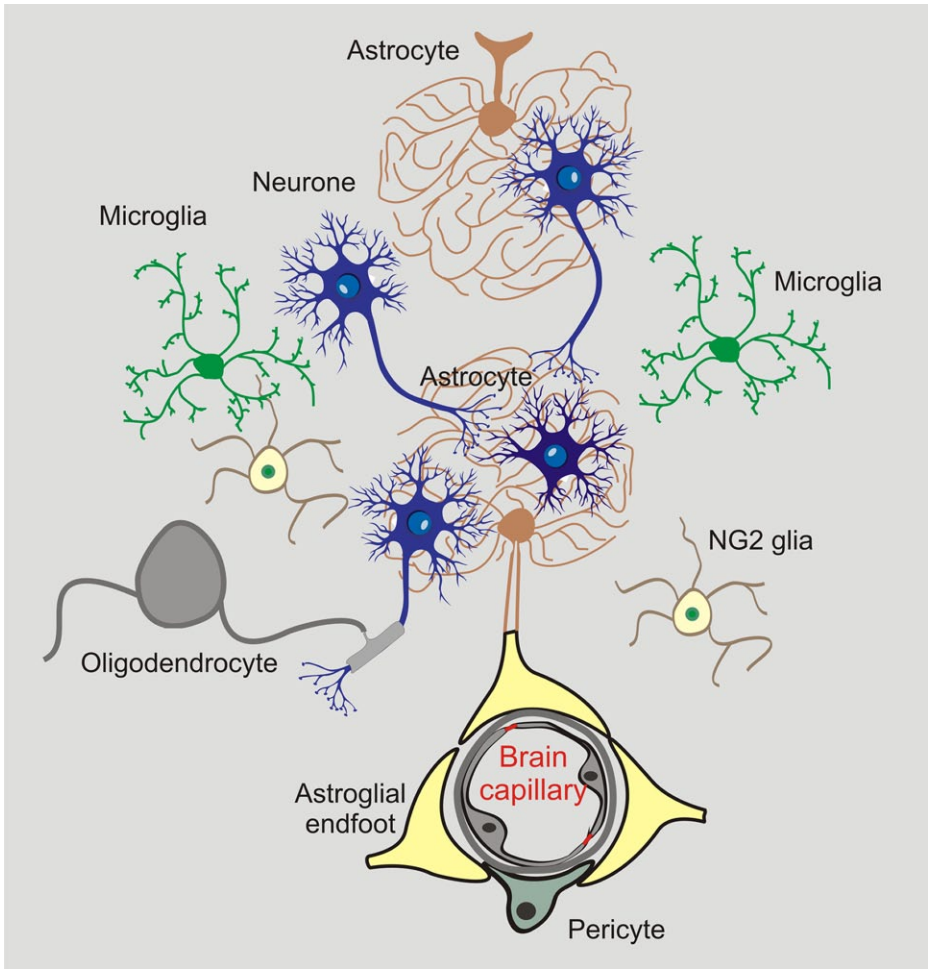

Figure 1. Multicellular nature of the central nervous system. The CNS tissue is composed of many cell types of ectodermal (neural) and mesodermal origin. The neural cells include neurons, astrocytes, oligodendrocytes, and NG2 glia. Cells of mesodermal origin are represented by microglia, endothelial cells, and smooth muscle cells of blood vessels. Blood flow through brain capillaries is controlled by pericytes (Hamilton and others 2010), which in the CNS may also be of neural descent.

contributing to neuropathology. Among all these multiple cell types, however, the neuroglia, being the main homeostatic and defense element of the CNS assumes particular importance in evolution of neurological diseases.

Neuroglia: The Homeostatic and Defensive Arm of the CNS

Evolution of Housekeeping Neural Cells

Evolution of the CNS that progressed from a diffuse nervous system in early multicellular organisms through centralization that occurred in the early invertebrates because of fusion of neural ganglia to the multilayered CNS of vertebrates required continuous specialization of the cellular elements. The very first glia that emerged in nematodes assisted formation of the sensory organs (Bacaj and others 2008; Hartline 2011; Reichenbach and Pannicke 2008); at the subsequent phylogenetic steps glial cells (mainly of astroglial appearance) became highly specialized and assumed full responsibility for nervous system homeostasis in insects, crustaceans and mollusks (Verkhratsky and Butt 2013). Emergence of chordate coincided with the fundamental rearrangement of the CNS architecture: assembly of ganglia was substituted by the layered brain. This was the result of an appearance of a new type of glial cell, the radial glia, which became the focal point for neurogenesis and migration of newly born neural cells to their appropriate positions within appropriate layers (Rakic 2003). In ancient ancestors of vertebrates (in echinoderms and in early hemichordate) as well as in early vertebrates (in some chondrichthian or teleost fish) the radial glia is the only glia in existence; in these species the parenchymal glia

(that attained such a high degree of diversification in invertebrates) are absent. Increase in the thickness of the neural tube triggered a new wave of glial evolution and in higher vertebrates multiple types of parenchymal astrocytes have developed (Reichenbach and others 1987).

The second major type of glia, the myelinating cells (oligodendrocytes, and oligodendroglia-related NG2 cells in the CNS and Schwann cells in the periphery) similarly appeared early in evolution (Bullock 2004; Hartline and Colman 2007; Roots 2008). The most ancient glial structures enwrapping axons with many layers of membranous lamellae emerged in annelids and crustacean; incidentally the fastest velocity of nerve impulse propagation of 210 m/s has been detected in prawns of genus *Penaeus* (Xu and Terakawa 1999). Myelin proper appeared later in early vertebrates; with placoderms (extinct early jawed armored fish that lived in the early Silurian period ~420 million years ago), being arguably the first species acquiring myelinated nerves (Zalc and others 2008).

The microglial cells, which are migrants from the myeloid tissue to the brain, invaded the nervous tissue at the early evolutionary stages being present in annelids and mollusks; in both species the microglial cells undergo characteristic modification that turn the primary macrophages into resident innate immune cells of the nervous system (Kettenmann and others 2011).

Brain Homeostasis: The Fundamental Function of Neuroglia

Neuroglial cells are disseminated in every part of the CNS; their densities, morphological appearances and physiology differ significantly between CNS regions, and yet their main function, maintenance of stable CNS environment (i.e., homeostasis), is vigorously pursued throughout.

Astrocytes, which are arguably the most diverse glia, are highly versatile cells contributing to all levels of CNS homeostasis from molecular (by balancing the composition of the interstitial fluid) to subcellular (e.g., by regulating synaptogenesis and modulating synaptic transmission), cellular (by controlling neurogenesis and neural cells development), organ (by creating astrogliovascular units and defining the cytoarchitecture of gray matter) and system (being involved in sleep regulation and systemic chemosensitivity). Astrocytes in particular regulate many aspects of CNS neurotransmission being often the central foci for neurotransmitters metabolism and trafficking. In particular, astrocytes are fundamental for maintaining glutamatergic and GABA-ergic transmission by supplying neurones with the neurotransmitter precursor glutamine and regulating extracellular glutamate concentration; similarly astrocytes are central for regulation CNS adenosine by virtue of astroglia-specific adenosine kinase (see Boison and others 2010; Kettenmann and Ransom 2013; Verkhratsky and Butt 2013 for details).

Oligodendrocytes myelinate axons of central neurones in both grey and white matter, thus being a critical element for brain connectome (Fields 2014; Zatorre and others 2012). Myelination of axons not only speeds up the nerve impulse propagation and possibly saves energy (due to limiting the area of ion transfer to nodes of Ranvier) but also allows for miniaturization of the nervous system, which seems to be critical for evolution of highly connected CNS in mammals. Myelin sheath is a dynamic structure that can be remodelled in various forms of neuroplasticity (Fields 2005; Snaidero and others 2014). Oligodendrocytes also contribute to periaxonal ion and neurotransmitter homeostasis, provide axonal metabolic support and are capable of rapid dynamic regulation of the action potential propagation (Fields 2008a). The NG2 glia, lineage-related to oligodendrocytes, may be involved in myelination/remyelination in the adult brain as well as contribute to general housekeeping (Nishiyama and others 2009; Richardson and others 2011).

Microglial cells originate from c-kit+ erythromyeloid precursors present in the extra-embryonic yolk sac (Kierdorf and others 2013), which invade neural tube very early (at E10 in mice (Ginhoux and others 2010)) in embryogenesis. Microglial precursors disseminate throughout the CNS and undergo transformation into ramified microglia, characterised by specific morphology (small cell body and long, thin motile processes) and physiology (expression of extended complement of receptors to neurotransmitters and neurohormones, as well as classic "immune" receptors, such as Toll-like receptors, and receptors to chemokines/cytokines; Kettenmann and others 2011). Microglia contribute to CNS development by removing apoptotic neurones and shaping neuronal networks through synaptic tripping; loss of microglial function in embryogenesis may be one of the primary mechanisms of neurodevelopmental disorders such as autism (Collingridge and Peineau 2014; Kettenmann and others 2013; Tremblay and others 2011).

Neuroglia Form the Defense System of the Brain

Neuroglial cells instantly react to every kind of insult to the CNS tissue by mounting a homeostatic response. In brain ischemia, for example, astroglia exert neuroprotection by removing excitotoxic factors (K^+ ions and glutamate), scavenging reactive oxygen species (astrocytes are sole vendors of the main reactive oxygen species [ROS] buffers glutathione and ascorbic acid) and supporting neuronal metabolism (Verkhratsky and Butt 2013). Besides the homeostatic response, neuroglia possess an evolutionary conserved program of profound remodeling

in response to polyetiological lesions to the CNS, generally defined as reactive gliosis (Burda and Sofroniew 2014; Pekna and Pekny 2012). The reactive gliosis is formally classified into reactive astrogliosis, proliferative response of NG2 cells and activation of microglia. All these gliotic processes contribute to the tissue response to the damage; this response further includes reactions of non-neural cells and cells invading CNS parenchyma as a consequence of, for example, disruption of blood-brain barrier (Burda and Sofroniew 2014). Reactive gliosis is a complex and multistage process that is fundamentally survivalistic, being aimed at neuroprotection and regeneration; glial reactivity is disease specific and produces multiple phenotypes of activated neuroglial cells, which contain the damage (for example by making the glial scar), remove pathogens and assist in postlesion regeneration of the neural networks (Burda and Sofroniew 2014; Pekna and Pekny 2012; Pekny and others 2014; Sofroniew 2009; Sofroniew and Vinters 2010).

Gliopathology: Central Element of Neurological Diseases

Conceptually, a disease (from Old French *desaise* "lack of ease") can be defined as a failure of homeostasis (in which homeostasis is considered in its broad sense embracing all levels of organisation of the living system). It is therefore little surprising that neuropathology, to a great extent, represents the impotence of neural homeostatic system, that is, neuroglia. Failure of neuroglia to protect, to contain and to resolve the damage lies at the very core of pathological progression and defines the neurological outcome. When and if neuroglial homeostatic and defensive mechanisms are exhausted, the neural tissue dies (for gliocentric concept of neuropathology, see Coulter and Eid 2012; De Keyser and others 2008; Giaume and others 2007; Heneka and others 2010; Parpura and others 2012; Rajkowska and Miguel-Hidalgo 2007; Rodríguez and others 2009; Seifert and Steinhäuser 2013; Verkhratsky and others 2013a; Verkhratsky and others 2012).

Often, neuroglia represent a primary pathological element of the disease. For example, sporadic mutations of astroglia-specific glial fibrillary acidic protein (GFAP) cause Alexander disease manifested by severe degeneration of white matter or leukodystrophy (Messing and others 2012). Similarly expression of mutant MECP2 gene in astrocytes affects neurodevelopment, whereas their expression in microglia induce neurotoxic phenotype; thus both types of glia participate in pathogenesis of Rett syndrome (Maezawa and Jin 2010; Maezawa and others 2009). Another mutant gene Hoxb8 associated with trichotillomania (or hair pulling disorder) is expressed exclusively in microglia, and at least in mice microglial pathological remodeling causes compulsive behavior (Chen and others 2010). Astrocytes are primary targets for many (if not all) toxic encephalopathies (Butterworth 2010b), the ammonium toxic encephalopathy being a noteworthy example. Hyperammoniemia, which results mostly from liver failure but also from urea cycle deficiencies or Reye's syndrome causes polymorphic mental and behavioural symptomatology represented by confusion, forgetfulness, irritability and alterations of consciousness such as lethargy, somnolence and, in the terminal stages, coma. Astrocytes are primary targets of hyperammoniemia; and related encephalopathy can be regarded as a toxic astrogliopathology. The astrocyte-specific enzyme, glutamine-synthetase provides the main pathway for ammonia detoxification. Accumulation of ammonium by astrocytes increases activity of glutamine synthetase and alters astroglial homeostatic functions compromising K^+, glutamate and water homeostasis, which, in turn, causes aberrant neurotransmission (that underlies psychotic symptoms) and (in terminal stages) brain edema (Brusilow and others 2010; Butterworth 2010a; Rangroo Thrane and others 2013; Rose and others 2013).

In many other pathologies, neuroglial contribution appears to be secondary, mounting in response to polyetiological lesions. Reactive astrogliosis for example, occurs in a wide variety of neuropathologies from acute trauma and stroke to neurodegeneration (Burda and Sofroniew 2014; Heneka and others 2010; Pekna and Pekny 2012). Importunately, astroglial reactivity results in an appearance of numerous phenotypes, which are disease specific (Pekny and others 2014). Reactive astrogliosis is an important component of progression and resolution of neuropathology, and suppressing astroglial reactivity increases neuronal vulnerability, exacerbates pathological development and alters postlesion regeneration (Burda and Sofroniew 2014; Pekny and others 2014; Sofroniew 2009). Similarly, activation of microglia appear as a multistage and multivector process that results in emergence of multiple neuroprotective as well as neurotoxic cellular phenotypes (Kettenmann and others 2011; Ransohoff and Perry 2009). Finally, several types of neuropathology are associated with glial asthenia, atrophy or degeneration. Here, astrocytes, for example, reduce their territorial domain with a decrease of synaptic coverage and homeostatic prowess, or else degenerate and die. Astrodegeneration is characteristic for neuropsychiatric diseases and seemingly contributes to the majority of neurodegenerative processes (Verkhratsky and others 2012; Verkhratsky and others 2013b).

Neuroglia in Neurodegenerative Diseases

Gliopathology in neurodegenerative diseases is represented by gliodegeneration (i.e., loss of glial function)

and by glial reactivity, the latter being often initiated by emergence of specific lesions.

In neurodegeneration associated with toxic encephalopathies, for example, astrocytes frequently are the primary pathological element; the progression of the disease is defined by down-regulation of astroglial glutamate transporters, which results in accumulation of extracellular glutamate and glutamate excitotoxicity. This mechanism is central in poisoning with metals, such as lead, aluminum, or manganese. Similarly, astroglia-specific glutamate homeostasis appears as a primary target in methylmercury-induced encephalopathy (also known as Minamata disease (McAlpine and Araki 1958)), in which accumulation of methylmercury into astrocytes inhibits glutamate, glutamine and cystine transporters, thus compromising glutamate homeostasis and inducing excitotoxic neuronal death, which in turn defines symptomatology manifested by cognitive decline, impaired vision and hearing, as well as motor symptoms (Ni and others 2012; Yin and others 2007).

Another example of astroglial loss of function as a primary pathogenic step is the Wernicke encephalopathy, the thalamocortical neurodegeneration, which appears as a substrate for Korsakoff syndrome (ante- and retrograde amnesia, apathy and confabulation (Korsakoff 1889; Wernicke 1881–1883). In this pathology, a severe down-regulation of astroglial glutamate transporters induces a massive neuronal death; astrocytes also display signs of morphological degeneration. Astrodegeneration in combination with astrogliotic response is observed in the HIV-associated dementia, which is the primary microglial infectious pathology, is associated with astroglial atrophy and decrease in astroglial population, which correlates with cognitive impairment (Thompson and others 2001). Signs of astroglial atrophy and death have been identified in non–Alzheimer's disease dementias in combination with astrogliosis, especially in frontotemporal and thalamic dementia (Broe and others 2004; Kersaitis and others 2004; Potts and Leech 2005).

Astrodegeneration and astroglial asthenia are central factors for pathogenesis of amyotrophic lateral sclerosis (ALS). In experimental models of ALS (expressing disease related human mutant gene of superoxide dismutase 1, hSOD1) atrophy and death of astrocytes precede damage to motor neurones and clinical symptoms, whereas selective silencing of *hSOD1* gene in astrocytes delays ALS progression (Rossi and others 2008; Rossi and Volterra 2009; Yamanaka and others 2008). In Huntington disease loss of astroglial glutamate uptake as well as increased astroglial release of glutamate contributes to neurodegenerative progression (Behrens and others 2002; Lee and others 2013).

Neuroglia in Alzheimer's Disease

Progressive dementia with specific histopathology represented by senile plaques (extracellular depositions of β-amyloid) and interneuronal tangles resulted from abnormal phosphorylation of tau protein has been named "Alzheimer's disease" (AD) by Emil Kraepelin (Kraepelin 1910) in honour of his pupil and subordinate Alois Alzheimer who described the family form of this dementia (Alzheimer 1907). The leading hypothesis of AD regards overproduction of β-amyloid or failure of its clearance as a main pathogenetic step (Braak and others 1998; Gerlai 2001; Hardy and Selkoe 2002; Karran and others 2011; Korczyn 2008). This hypothesis, however, currently tries to weather a mounting critique (Castellani and others 2009; Castellani and Smith 2011; Hardy 2009). A pathological role for astroglia in the disease progression was foreseen by Alzheimer himself, who described glial cells closely contacting damaged neurons and populating senile plaques (Alzheimer 1910).

Atrophy and Reactivity of Astrocytes in Animal Models of AD

The notion of atrophic changes in astroglia that appear at the early stages of AD emerged in recent years following in depth morphological studies of the brains of transgenic animal models. Couple of dozens of mice AD-like strains have been produced in a recent decade; all of them bear mutant genes associated with family AD in different combinations (Gotz and others 2012; Oddo and others 2003). Most of these mice express mutant genes for amyloid precursor proteins and or presenilins, which allows production of β-amyloid in animals, wild types of which are lacking this pathway; the brains of these mice therefore become overloaded with β-amyloid and form *bona fide* senile plaques. Some of the transgenic AD mice carry in addition mutant gene for tau protein and hence develop both senile plaques and intraneuronal tangles.

Reduction of astroglial profiles (as revealed by immunostaining with antibodies against GFAP and glutamine synthetase [GS]; Fig. 2) together with decrease in astroglial complexity and number of principal and secondary processes have been quantified in hippocampi from mice with experimental amyloidosis (the PDAPP-J20 mice expressing mutant APP; Beauquis and others 2013; Beauquis and others 2014) and in 3xTg-AD mice that display senile plaques and tangles (Olabarria and others 2010; Verkhratsky and others 2010). Importantly, these atrophic changes occurred before the emergence of amyloid plaques (i.e., before 12 months of age for 3xTG-AD mice); at the same time total number of astroglial cells remained stable in all age-groups (up to 24 months). Signs of astroglial atrophy have been found in other regions of the brain (Fig. 2); in particular they appear very early (~1 month of age) in entorhinal cortex (Yeh and others 2011), and quite early (~6 months old) in prefrontal cortex (Kulijewicz-Nawrot and others 2012).

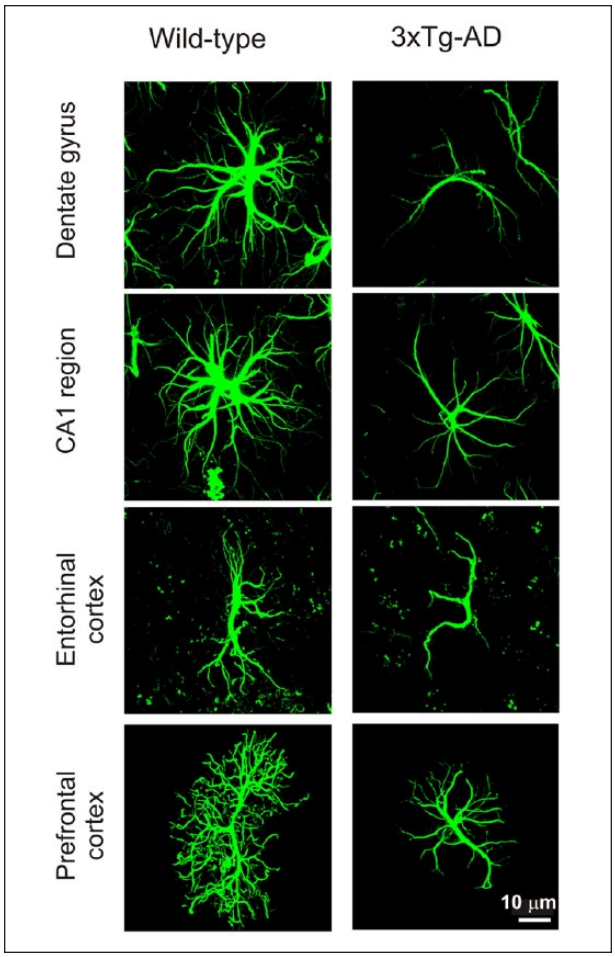

Figure 2. Atrophy of glial fibrillary acidic protein (GFAP)-positive astroglial profiles in the main mnesic areas associated with Alzheimer's disease. Confocal micrographs illustrate decreased GFAP-positive astroglial profiles in the hippocampal dentate gyrus and Corni ammonia 1 (CA1) regions as well as in the entorhinal cortex and prefrontal cortex in 3xTg-AD mice compared with control animals.

In AD animal models, astrodegenerative changes are complemented by astroglial reactivity. Reactive, hypertrophic astrocytes occur in hippocampus in response to development of senile plaques and perivascular β-amyloid deposits, with which reactive astrocytes are associated (Olabarria and others 2010). Reactivity of astroglia in AD animals is of a mild variety with preservation of astroglial domains and no signs for glial scar formation (Fig. 3). The reactive astrocytes show reduced expression of GS (Fig. 4; Olabarria and others 2011) and generate aberrant Ca^{2+} signals represented by spontaneous Ca^{2+} oscillations and abnormal Ca^{2+} waves (Kuchibhotla and others 2009). Astroglial reactivity however was not uniform throughout the brain; accumulation of extracellular β-amyloid failed to induce reactive astrogliosis in entorhinal and prefrontal cortices (Kulijewicz-Nawrot and others 2012; Yeh and others 2011).

Increased astroglial reactivity may delay evolution of β-amyloid burden. In Tg2576 mice expressing the APP_{Swe} mutation (Hsiao and others 1996) β-amyloid pathology develops relatively slower when compared with APP/PS1, PDAPP-J20 and 3xTg-AD mice. The β-amyloid deposits in these mice are morphologically similar to those detected in humans (Yamaguchi and others 1998) and are represented by fleecy, granular, cored, and diffused amyloid plaques (Fig. 5). Phenotypically, the Tg2576 mice are similar to a prodromal stage rather than to full AD (Ashe and Zahs 2010). The slow progression of β-amyloid pathology on Tg2576 mice is associated with prominent early astrogliosis as demonstrated by strong GFAP-immunoreactivity, which is observed before the appearance of β-amyloid plaques. The density of reactive astrocytes changes with age and shows regional differences in distribution, morphological phenotype as well as localization in relation to β-amyloid plaques. At the advanced age (17-22 months old) the double immunolabeling with antibodies for β-$amyloid_{1-42}$ and GFAP demonstrated the presence of mainly atrophic and fewer reactive astrocytes; these latter were concentrated around β-$amyloid_{1-42}$ stained plaques, while the atrophic astrocytes were observed distant to the amyloid plaques (Fig. 6A, B). Decrease in astroglial reactivity therefore is inversely correlated with extracellular β-amyloid load. At the same time inhibition of reactive astrogliosis in the AD mouse model significantly increased β-amyloid load and exacerbated pathological progression (Kraft and others 2013).

Incidentally, GFAP-positive astrocytes in the hippocampus of Tg2576 mice express α7-acetylcholine nicotinic receptors (nAChRs). These nAChRs expressing astrocytes are detectable only in older Tg2576 mice, being undetectable neither in wild type controls nor in young transgenic animals. The α7 nAChRs were identified in astrocytes surrounding β-amyloid plaques in the cortical regions of postmortem brains of sporadic AD and family AD; with the number of α7 nAChR expressing astrocytes being significantly higher in postmortmem brain tissue from AD patients with APP_{Swe} mutation in comparison to sporadic AD patients, suggesting that this subpopulation of astrocytes may contribute to a reactive response to β-amyloid deposition (Yu and others 2005).

Nicotinic α7 receptors contribute to learning and memory and are known to protect from and interact with various forms of β-amyloid (Lilja and others 2011; Ni and others 2013; Shimohama and Kihara 2001). It is hence possible that α7 nAChR-expressing cells represent a subpopulation of astrocytes involved in neuroprotection and repair. This is further supported by our recent findings of an increased density of α7 nAChR-expressing astrocytes in the hippocampus of Tg2576 mice that

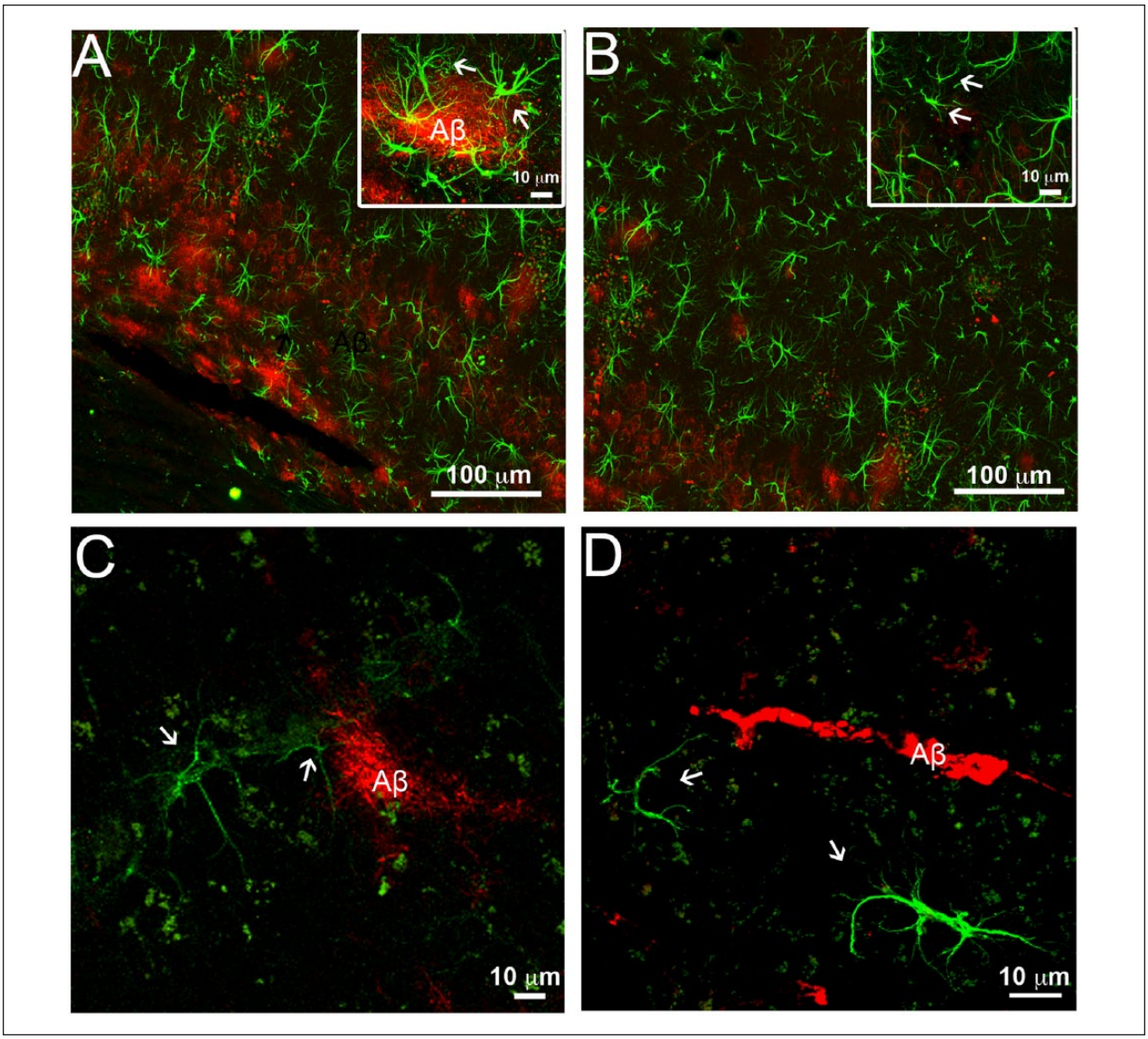

Figure 3. β-Amyloid depositions trigger gliotic response in associated astrocytes in the hippocampus but not in the entorhinal cortex. (A, B) Confocal images of hippocampal preparations labeled for glial fibrillary acidic protein (GFAP; green) and β-amyloid (red) illustrating differential changes in GFAP profiles in astrocytes in close association with Aβ plaques (A) and atrophic profiles of astrocytes distant from β-amyloid deposits (B) in 3xTg-AD mice. (C, D) Confocal dual labeling images (GFAP in green and β-amyloid in red) showing absence of reactive response of astrocytes in the entorhinal cortex of 3xTg-AD mice around perivascular vascular β-amyloid deposits (C) and β-amyloid plaques (D).

received neural stem cell implants (Fig. 6C); this increase was also accompanied by improved cognitive performance (Lilja, Malmsten, Verkhratsky, Nordberg, Marutle, own observations).

Molecular mechanisms triggering astroglial reactivity remain debatable. There are indications that soluble β-amyloid induces abnormal Ca^{2+} oscillations in cultured primary astrocytes (Abramov and others 2003; Abramov and others 2004), although these results were not universally confirmed (Grolla and others 2013; Ronco and others 2014). Chronic exposure of cultured astrocytes to β-amyloid resulted in significant changes in the Ca^{2+} signaling toolkit in hippocampus (up-regulation of metabotropic glutamate receptors and $InsP_3$ receptors) but not in the entorhinal cortex (Grolla and others 2013). The $InsP_3$ receptors are fundamental for inducing astroglial reactivity (Kanemaru and others 2013), and their insensitivity to β-amyloid may contribute to the absence of reactive astrogliosis observed in the entorhinal cortex of 3xG-AD mice.

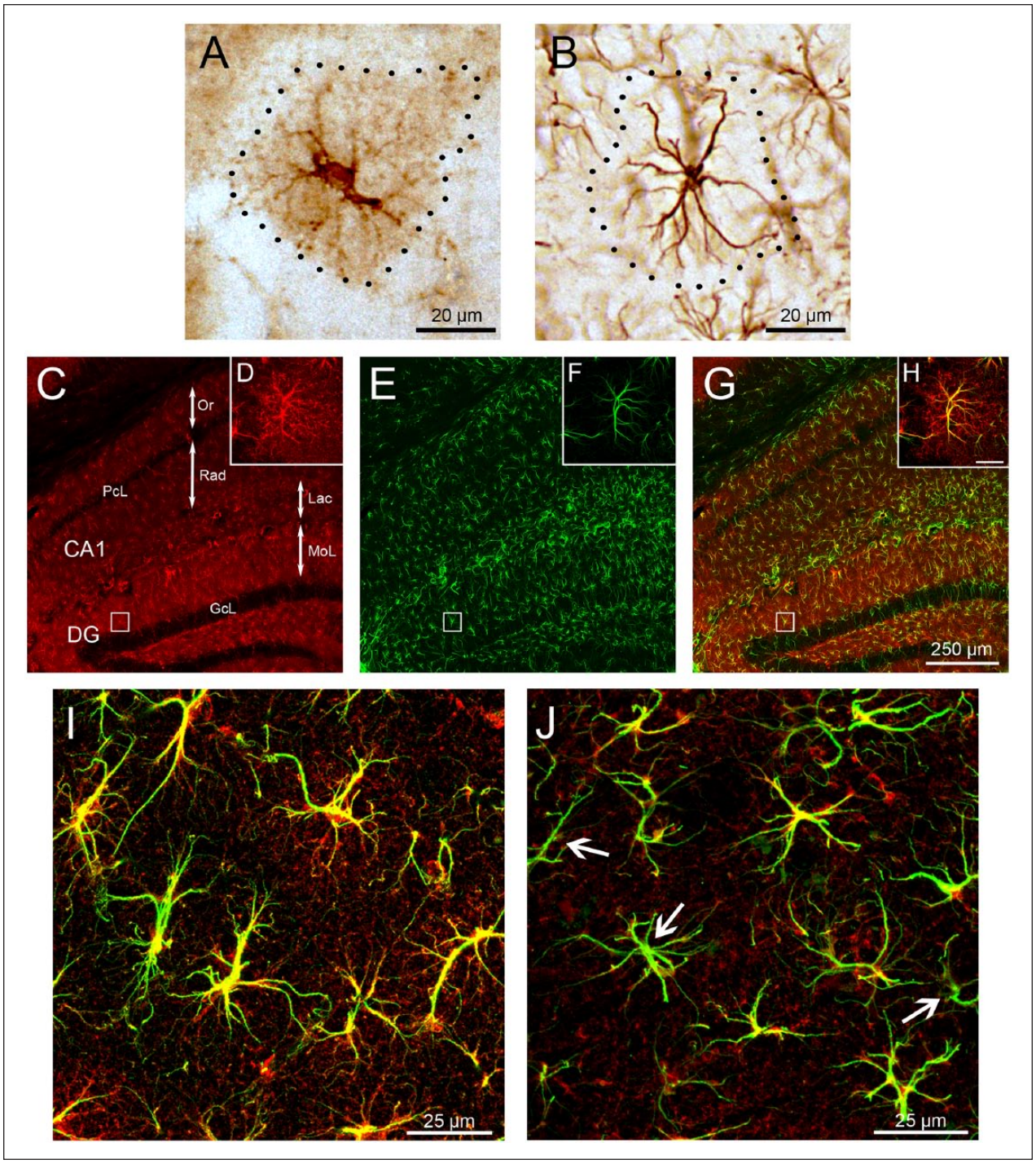

Figure 4. Down-regulation of glutamine synthetase (GS) expression in hippocampal astrocytes in AD mice. (A, B) Light microscopy images of GS-positive (A) and glial fibrillary acidic protein (GFAP)-positive (B) astrocytes. (C, E, G) Confocal images of hippocampal preparation labeled for GS (C, red), GFAP (E, green), and their co-localization (G, yellow). (D, F, H) High magnification confocal images illustrating the co-expression of GS and GFAP. (I, J) Ubiquitous co-expression of GS and GFAP in wild type control mice (I) and down-regulation of GS expression (astrocytes lacking GS are indicated by arrows) in 3xTg-AD mice (J). DG = dentate gyrus; GcL = granule cell layer; Lac = stratum lacunosum moleculare; MoL = molecular layer; Or = stratum oriens; PcL, pyramidal layer; Rad, stratum radiatum. Modified with permission from Olabarria and others (2011).

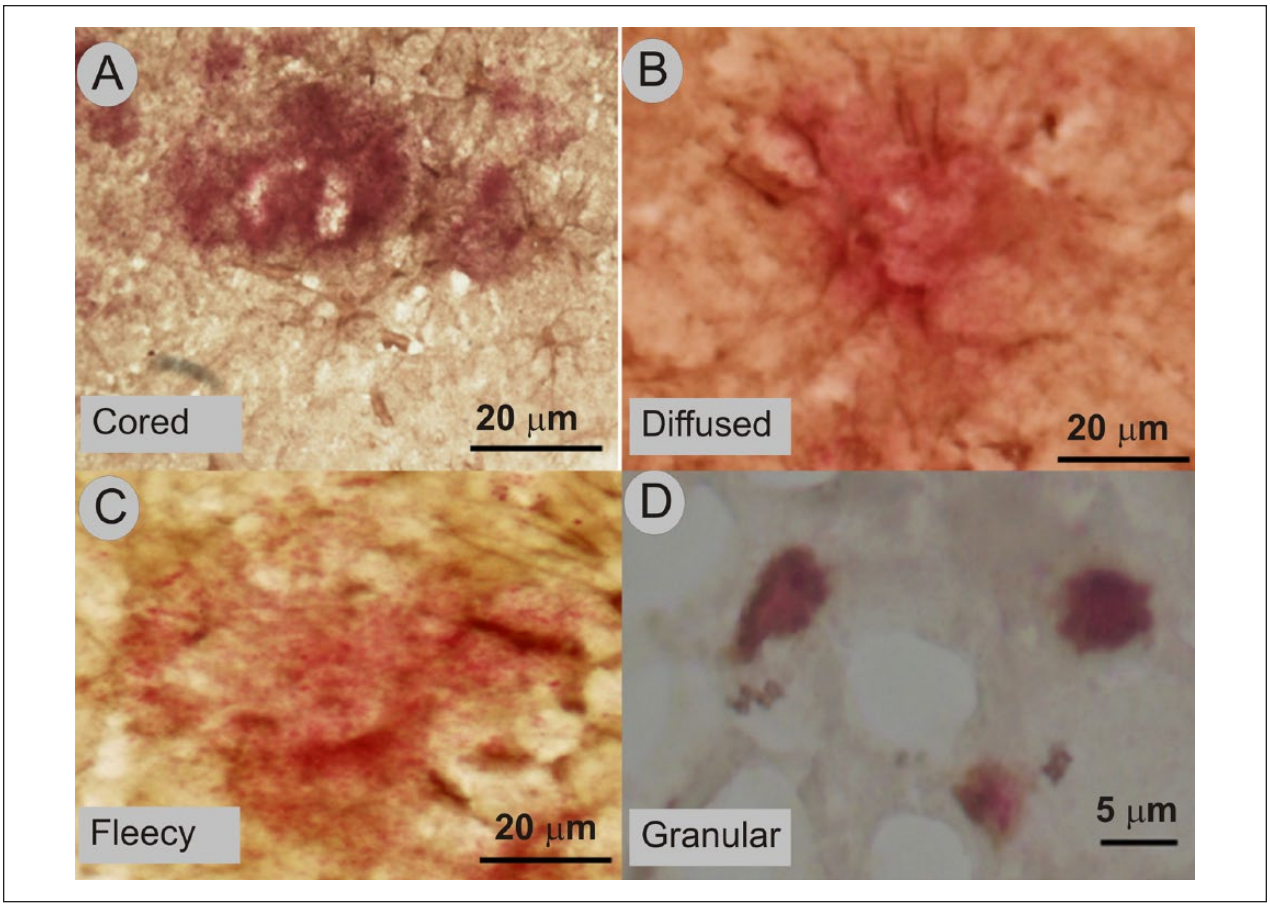

Figure 5. Heterogeneity of β-amyloid plaques in the brains of Tg2576 mice with Alzheimer's disease (AD). Immunohistochemical labeling of (A) cored and (B) diffuse β-amyloid$_{1-42}$ plaques, and (C) fleecy and (D) granular β-amyloid$_{1-42}$ deposits in Tg2576 mice brain (Voitenko, Marutle and Nordberg, own observations).

Astrocytes in Human AD

Astroglial reactivity (defined by an increase in GFAP or S100β expression) was frequently described in the AD post-mortem tissues (Beach and McGeer 1988; Griffin and others 1989; Meda and others 2001; Mrak and Griffin 2005), and even some correlation between increased GFAP levels and the Braak stage of AD were claimed (Simpson and others 2010). Incidentally, however, no correlation between reactive astrogliosis and β-amyloid load was identified (Simpson et al., 2010). Other studies however found no differences in the expression of GFAP between demented and non-demented brains (Wharton and others 2009).

In vitro binding assays in postmortem AD brain have demonstrated an increased [^{3}H]-deprenyl binding (indicative of astroglial activation) in the hippocampus, paralleled by an increase in [^{3}H]-PK11195 (indicative of microglial activation) binding as well as [^{3}H]-PIB (depicting emergence of fibrillar β-amyloid plaques) binding in the frontal cortex (Marutle and others 2013). Quantitative autoradiography binding studies have shown a clear lamination pattern with high [^{3}H]-PIB binding in all layers and [^{3}H]-deprenyl binding in superficial layers of the frontal cortex; in the hippocampus in contrast a low binding to fibrillar β-amyloid by [^{3}H]-PIB and high binding to activated astrocytes with [^{3}H]-deprenyl was detected throughout (Marutle and others 2013).These observations suggest a distinct regional pattern for astroglial activation in AD brain.

Modern molecular imaging provides a new tool to study the brain and to better understand functional disturbances as well the time course of different pathological changes. The introduction of β-amyloid positron emission tomography (PET) imaging for visualizing of fibrillar amyloid plaques in the brain (Klunk and others 2004; Nordberg and others 2010) has provided new and valuable insight into the dynamics and the time course of deposition of fibrillar β-amyloid in the brain in the course of transition from preclinical to clinical stages of AD.

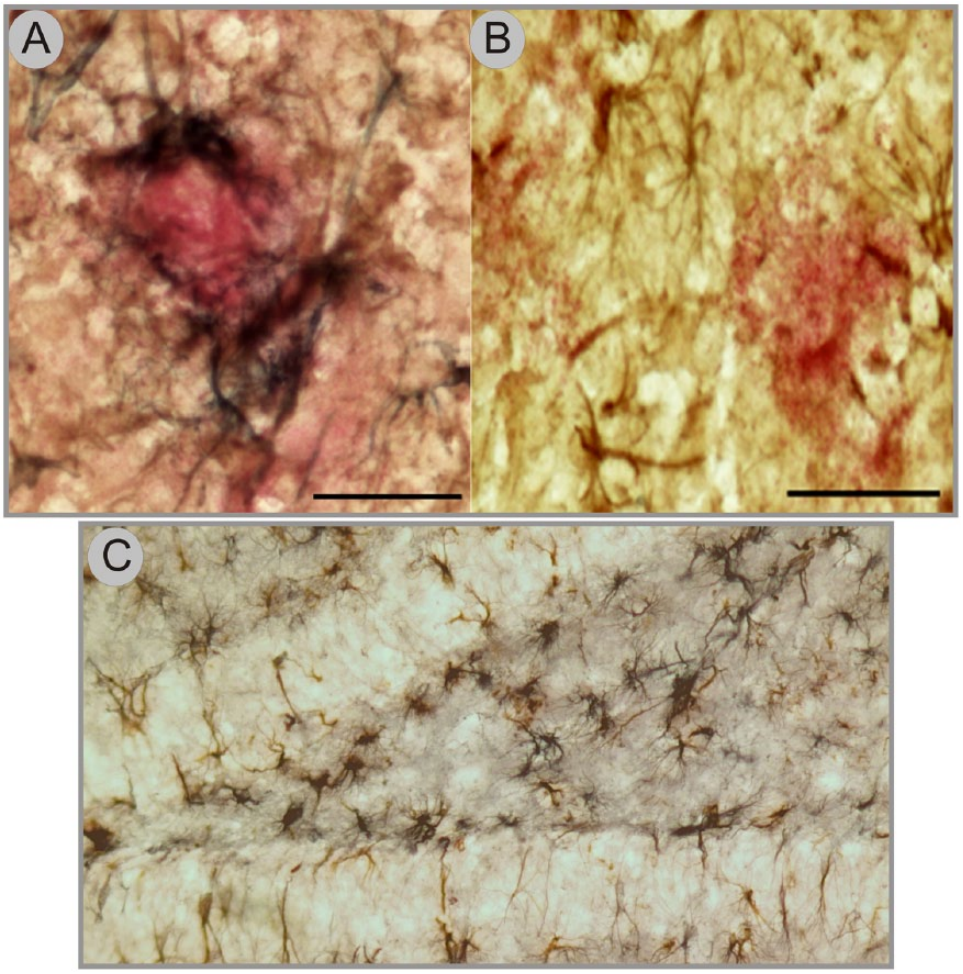

Figure 6. Different types of glial fibrillary acidic protein (GFAP)-positive astrocytes are present in the brain of Tg2576 mice. (A, B) Images of GFAP-positive reactive astrocytes associated with β-amyloid plaques (A) and distant to the plaques (B) in the cortex of Tg2576 mice. (C) Double immunolabeling with antibodies for α7 nAChRs and GFAP demonstrated an abundant presence of α7 nAChR/GFAP-positive astrocytes in the dentate gyrus of 8-month-old Tg2576 mice following intrahippocampal neural stem cell implantation. GFAP-positive reactive astrocytes are labeled brown and α7 nAChR/GFAP-positive cells are labeled black at 20× magnification.

For visualization of early signs for glial activation in AD brains a PET technique using ^{11}C-deuterium-L-deprenyl (^{11}C-DED) to measure the binding to monoamine oxidase B in the astrocytes has been developed (Fowler and others 1997); this tracer was used for example in visualizing astroglial reactions in Creutzfelt-Jacob disease (Engler and others 2012), amylotrophic lateral sclerosis (Johansson and others 2007) and epilepsy (Kumlien and others 2001). These studies showed an increase in ^{11}C-DED signal in the parietal, occipital and frontal cortices in Creutzfeldt-Jacob disease (Engler and others 2012); similarly increased ^{11}C-DED binding was identified in the white matter and in pons in amyotrophic lateral sclerosis. PET studies with ^{11}C-DED have also demonstrated an association of increased binding with normal brain aging (Fowler and others 1997).

When using a multitracer PET concept consisting of ^{11}C-PIB (fibrillar β-amyloid), ^{18}F-FDG (cerebral glucose metabolism), and ^{11}C-DED (astroglial activation), the highest binding of ^{11}C-DED (highest astrogliotic response) was observed in patients with mild cognitive impairment (MCI) and high levels of fibrillar amyloid plaques in the brain (PIB+) reflecting prodromal AD in comparison to clinically demented AD patients and MCI patients with no obvious fibrillar β-amyloid plaques as well as to healthy age-matched controls (Fig. 7; Carter and others 2012). The *in vivo* PET observations are in agreement with earlier findings of gliosis in different cortical layers in

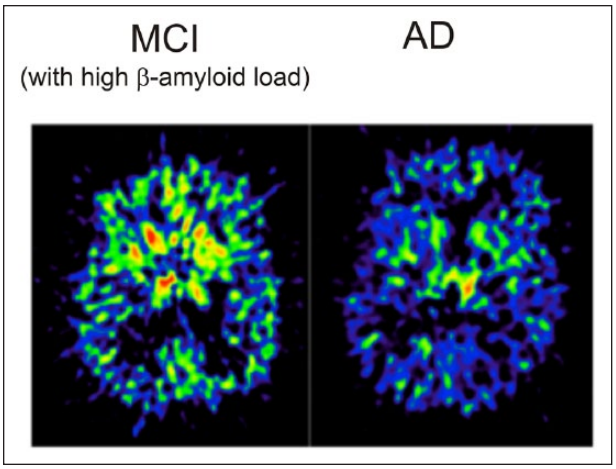

Figure 7. High astrogliosis in the brain of patient with mild cognitive impairment associated with high β-amyloid load indicative of prodromal AD (left panel) in comparison with clinically demented patient with Alzheimer's disease (AD; right panel). Representative parametric images of ^{11}C-D-deprenyl binding (that reports monoamine-oxidase activity in astrocytes) were obtained by position emission tomography. The patient with mild cognitive impairment (MCI) also showed high presence of fibrillar amyloid plaque as measured with ^{11}C-PIB (the status that could be identified as a prodromal AD). The positron emission tomography scans show sagittal sections of the brain at the level of basal ganglia. Color scale: red = very high, yellow = moderate high, green = high, blue = low ^{11}C-D-deprenyl binding. Photo courtesy A. Nordberg, Karolinska Institutet.

postmortem AD brain tissue (Beach and McGeer 1988). The observed different laminar distribution of fibrillar β-amyloid plaques and astrogliosis most probably represents processes evolving in parallel with different regional distribution and time course (Marutle and others 2013). These observations support the assumption that astrogliosis might be an early sign for histopathological changes in the course of AD and even might precede large deposition of fibrillar β-amyloid plaques in the brain. In presymptomatic AD mutations carriers high ^{11}C-DED binding is detected before amyloid plaques can be identified in the brain (Nordberg 2014). Recently, a significant negative correlation was observed between ^{11}C-DED binding and gray matter density in the parahippocampus in prodromal AD patients (Choo and others 2014).

Micro-PET studies in Tg2576 mice using ^{11}C-DED for detection of astrogliosis and ^{11}C-PIB and ^{11}C-AZD2184 for detecting fibrillar β-amyloid similarly revealed an increased ^{11}C-DED binding at age preceding emergence of plaques pathology (Rodriguez-Vieltez et al. submitted). Most importantly however, high level of astrogliosis was associated with MCI and prodromal AD, whereas the decline of astrogliotic response signaled development of cognitive deficits associated with clinically evident AD.

Oligodendroglial Decline?

The white matter occupies 50% of the human brain (Fields 2008b) and is a fundamental part of interneuronal connections dubbed "the brain connectome" (Sporns and others 2005), a name that is gaining in popularity. Oligodendrocytes are the major myelinating cell present in the white and in the gray matter in the CNS. Primary and/or secondary oligodendrocyte death and myelin damage occurs in most, if not all, CNS diseases including stroke, perinatal ischemia, multiple sclerosis, psychiatric disorders, traumatic injury and Alzheimer's disease (Matute 2010). In physiological aging white matter experiences the most substantial changes being reduced by ~11%, compared with only 3% decrease in the cortical volume (postmortem volummetry, Haug and Eggers 1991; or magnetic resonance imaging, Albert 1993); it has been claimed that 20% to 40% of myelinated axons seem to disappear from fiber tracts in senescent CNS (Lintl and Braak 1983). This loss in white matter goes in parallel with a (somewhat surprisingly) substantial increase in oligodendrocytes density with ~50% increase in oligodendroglial cells number in visual cortex of old monkeys when compared to adult (Peters and Sethares 2004); senescent oligodendrocytes also display altered morphology (Peters 1996).

Severe loss of white matter, which correlates with cognitive impairment, is also observed in AD (Bronge, 2002) with lesions being prevalent in early-stage AD at periventricular and deep white matter (Burns and others 2005). A high proportion of AD patients have prominent white matter degeneration (known as leukoaraiosis) and profound apoptotic death of oligodendrocytes (Brown and others 2000). This apoptotic death may be associated with aberrant Ca^{2+} homeostasis (Matute 2010). It has been also found that β-amyloid can either directly damage oligodendrocytes (Xu and others 2001). Injection of 1 nM β-amyloid into corpus callosum severely damaged oligodendrocytes and destroyed myelin (Jantaratnotai and others 2003). Aberrant Ca^{2+} homeostasis and increased sensitivity to glutamate damage was observed in olgodendrocytes from PS1 mutant AD model mice (Pak and others 2003), whereas in the 3xTg-AD mice region-specific alterations in myelination and in oligodendroglial profiles preceded emergence of β-amyloid plaques and intraneuronal tangles (Desai and others 2009).

Microglial Paralysis?

Microglial cells are intimately involved in developmental plasticity of the brain and the spinal cord and in providing multicomponent defence against polyaetiological insults to CNS (Gomez-Nicola and Perry 2014; Kettenmann and

others 2011; Kettenmann and others 2013). Activation of microglia, viewed as a sign of neuroinflammation, is widely considered to contribute to neurodegeneration; and indeed activated microglial cells appear at senile plaques in AD and are often prominent in other neurodegenerative disorders (Heneka and others 2010; Perry and others 2010; Perry and Teeling 2013). There are however mounting indications for functional insufficiency of activated microglia in neurodegenerative conditions, which, for example, is manifested in failed phagocytic capacity. Phagocytosis is impaired in activated microglia in the context of AD (Gomez-Nicola and Perry 2014; Krabbe and others 2013) and microglia cannot effectively remove misfolded prion proteins in prion disease (Hughes and others 2010). The predisposition for functional microglial asthenia can be associated with genetic variants of triggering receptor expressed on myeloid cells 2 (or TREM2), which is expressed in activated microglia and regulates pro-inflammatory/phagocytic balance (Guerreiro and others 2013) or with alterations in complement system (Lambert and others 2009).

Incidentally microglial densities are increased in normal ageing (Tremblay and others 2012) and at the early stages of neurodegenerative diseases such as AD (Rodríguez and others 2013; Rodríguez and others 2010) and HD (Tai and others 2007). Increase in microglial density in ageing is connected to the decrease in their function (Streit and Xue 2013); and possible early decrease in microglial density in neurodegeneration also indicates their asthenic transformation.

Pathological Potential of Gliodegeneration

Morphological atrophy of astrocytes at the early stages of the AD may have several pathologically relevant consequences. First and foremost this may result in decrease of astroglial synaptic coverage. Perisynaptic glial membranes that enwrap most (~70% in hippocampus) of the synapses in the CNS form "astroglial cradle" fundamental for maintenance of synaptic transmission through multiple molecular cascades sustaining homeostasis of the synaptic cleft and supplying neuronal terminals with neurotransmitter precursors (Nedergaard and Verkhratsky 2012; Verkhratsky and Nedergaard 2014). Reduced synaptic coverage may therefore compromise synaptic strength and even promote synaptic loss. This synaptic loss is generally considered to represent the earliest morphological symptoms of AD responsible for early signs of cognitive deficit (Coleman and others 2004; Terry 2000); moreover the degree of synaptic loss has been claimed to correlate with the severity of dementia (DeKosky and Scheff 1990; Samuel and others 1994). In addition asthenic astrocytes cannot support synaptogenesis (Eroglu and Barres 2010) thus affecting regeneration.

Astrodegeneration and loss of astroglial function compromise many other levels of CNS homeostasis thus contributing to AD progression. Astroglia are the main source of ROS scavengers such as glutathione and ascorbic acid, and hence astroglial weakness may exacerbate ROS-related damage. Similarly atrophic changes may affect the astrogliovascular unit as a whole thus lessening metabolic support of neurons and even promoting local ischemia. Progressive decrease in glucose utilization has been observed in functional brain imaging at the early stages of AD (Mosconi and others 2008), which also could be related to astroglial atrophy. Degenerative astrocytes may also contribute to vascular deficits frequently observed in AD (Bell and Zlokovic 2009; Zlokovic 2008). Finally, paralysis of astrogliotic response in certain brain areas may explain their high vulnerability to AD, as indeed entorhinal cortex appears to be the first to be affected by the disease. In the clinical evolution of the Alzheimer´s type pathology failure of astrogliotic response may be fundamental for the disease progression. Brain imaging experiments have demonstrated a correlation between a decrease in activated astroglia-associated signal and cognitive failure; in patients with high astrogliotic response the cognitive impairment remained mild even in the presence of β-amyloid load (Fig. 7; Carter and others 2012). Decrease in astrogliosis parallels with development of AD and precipitates terminal cognitive decline. Oligodendrocytes in AD also show the loss of function: despite very substantial increase in cell density the myelinating capabilities become impaired affecting inter-neuronal connectivity. Finally, deficient microglia, which lose their phagocytic capabilities may facilitate β-amyloid accumulation thus contributing to disease evolution.

Conclusions

The main function of neuroglia is preservation of CNS homeostasis in conditions of environmental pressure and in pathology. In that the defensive capabilities of neuroglia are fundamental for containing or facilitating the disease progression and neurological outcome. In neurodegeneration, neuroglial cells experience loss of important homeostatic and defensive functions and thus asthenic or paralytic neuroglia may define the progression of the disease.

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Note

1. This aphorism is sometimes attributed to Robert Remak (Baker 1953) and frequently to François-Vincent Raspail, which is stated in numerous articles (e.g., Tan and Brown 2006; Wright and Poulsom 2012), and even in Wikipedia (http://en.wikipedia.org/wiki/François-Vincent_Raspail); the original Raspail paper quoted in these sources (a paper on the development of starch in the grains of wheat: Raspail FV. 1825. Developpement de la fecule dans les organes de la fructification des cereales. Annales des sciences naturelles 6:224) does not contain the aphorism; we failed to find any original text written by Raspail that contains the text in question.

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