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Neuroglial Roots of Neurodegenerative Diseases?

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Abstract Neuroglia is critically important for controlling the brain homeostasis and for mounting the brain defence against pathological insults. Here, we overview recent data about the role of neuroglia in various types of neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, fronto-temporal dementia, Wernicke encephalopathy, amyotrophic lateral sclerosis and immunodeficiency virus-1-associated dementia). In all these forms of neurodegeneration, astroglia undergoes complex morphological and functional changes. The early and mid-term stages of neurodegenerative processes, and specifically of Alzheimer's disease, are associated with generalised atrophy of astroglia, whereas the later stages are characterised with an astrogliosis and microglial activation linked to neuropathological lesions such as senile plaques. Atrophic changes in astroglia may contribute to the initial cognitive deficits due to reduced glial synaptic coverage and decreased neuroprotection.

Keywords Astrocytes · Oligodendrocytes · Microglia · Alzheimer's disease · Parkinson's disease · Fronto-temporal dementia · Wernicke encephalopathy · Amyotrophic lateral sclerosis · Immunodeficiency virus-1-associated dementia · Neurodegeneration

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Introduction: Neurodegenerative Diseases—from Failed Network Connectivity to Neuronal Death

Neurodegeneration is a chronic process that results in a progressive loss of function, structure and number of neural cells, leading to generalised atrophy of the brain and profound cognitive deficit. The neurodegenerative diseases are rather specific to humans, being generally absent in animal species. Indeed, no animal naturally develops Parkinson's or Alzheimer's disease, and very rarely animals show signs of senile dementia. At the same time neurodegenerative pathologies profoundly affect the life of mankind, as indeed nothing can be more fearsome than loss of intellect and ultimate fading of human being into a helpless body.

The neurodegenerative process affects the connectivity of neural networks that is critical for the information processing and cognitive power [1–4]. Our knowledge about early events that occur at the onset of various neurodegenerative diseases is rudimentary, and yet, we may safely suggest that it all begins with synaptic weakness, disbalance of neurotransmission and functional disturbance of the information flow through the neural networks. These initial functional

abnormalities grow deeper with the disease progression leading to the loss of synapses, alteration of cellular structure and, eventually, to cell death. The brain atrophy, resulting from massive death of neural cells represents the final, irreversible stage of the neurodegenerative process, when the volume of the nervous tissue shrinks and neurological functions are severely impaired [5].

The cellular and molecular mechanisms involved in the development of neurodegenerative processes are many. Conceptually, the neurodegeneration can be viewed as a chronic and progressive failure of the brain homeostasis that finally assumes toxic proportions leading to massive cell demise.

Neuroglia Controls Brain Homeostasis and Defence

Neuroglia, which is classically divided into macroglia (astrocytes, oligodendrocytes and NG2 cells, all of ectodermal origin) and microglia (the resident macrophages of myeloid origin), represents the main cellular homeostatic element of the central nervous system. Macroglial cells control brain homeostasis at various levels, by regulating movement of water and ions, by controlling concentration of neurotransmitters in the extracellular space, by adjusting blood flow to local neuronal activity, by supplying neurones with metabolic substrates, by participating in synaptogenesis and synaptic maintenance and by contributing to neurogenesis and morphological plasticity of neural networks (see [6–15]).

In addition to controlling CNS homeostasis, neuroglia forms the intrinsic defence system of the brain and the spinal cord. This system is of specific importance for the immunologically privileged CNS tissue separated from the rest of the body by the blood–brain barrier [16]. The blood–brain barrier, sealed by tight junctions formed between endothelial cells, is under regulatory control of astroglia [17]. Insults to the brain or to the spinal cord trigger specific and evolutionary conserved glial defence response generally known as reactive gliosis. This response is manifested by a series of morphological and functional changes, which in astrocytes are represented by reactive astrogliosis [18, 19], in oligodendrocytes by Wallerian degeneration [20, 21] and in microglia by microglial activation [22, 23]. Conceptually, all these processes are aimed at isolating the damaged area, producing immune/inflammatory response against invading pathogens and assisting the post-lesion remodelling and recovery of the nervous tissue.

Neuroglia in Neurological Diseases

Being the main homeostatic and defence element of the brain neuroglia is intimately involved in the majority of neurological diseases. Every type of the brain insult triggers neuroglial reactions that are essential for the progression and outcome of the pathological process [24–27]. Astrocytes, for example, are critically involved in the development of brain trauma and stroke [8, 28]. The progression of the focal brain ischaemia is complex and includes rapid development of the ischaemic core, represented by the region of cellular pan-necrosis, and much slower formation of the ischaemic penumbra, which surrounds the zone of infarction. The expansion of the infarction zone through the penumbra takes days and the degree and velocity of this expansion is very much determined by the astrocytes. The astroglia is, in general, resistant to the ischaemia and excitotoxicity. Astrocytes can survive in the penumbra where they continue to perform their homeostatic functions acting as a neuroprotectors [8]. First and foremost, astroglia accumulates extracellular glutamate thus counteracting excitotoxicity [29], astrocytes scavenge reactive oxygen species, and by virtue of anaerobic processes, astrocytes produce lactate [7], which can sustain neuronal metabolism in the penumbra. In conditions of severe insults, however, astrocytes can become neurotoxic and contribute to cell death [26]. In particular, astrocytes can become a source of glutamate that can be released through several pathways (e.g. through plasmalemmal channels such as hemichannels, volume-sensitive Cl^- channels and $P2X_7$ receptors; through Ca^{2+}-induced exocytosis or via reversed glutamate transporters [30–34]). Astrocytes can even facilitate the spread of death signals, for example, by propagating waves of glutamate release [35]. In fact, the extension of necrotic zone through the penumbra may demarcate the primary extension of astroglial failure, which in turn determines the time-progression and severity of neurological deficit.

Similarly, oligodendroglia is central to the ischaemic damage of the white matter. Death of oligodendrocytes inevitably leads to axonal disintegration and therefore ischaemic insult to the white matter triggers disruptions of nerve fibres and causes severe functional disabilities. Oligodendrocytes, and in particular, oligodendroglial precursors are very sensitive to ischaemia and glutamate excitotoxicity. Even short periods of anoxia/ischaemia result in a complete loss of oligodendroglial ion homeostasis and Ca^{2+} overload toxicity [36, 37]. These toxic Ca^{2+} loads are mediated through activation of AMPA/NMDA ionotropic glutamate receptors and possibly through opening of $P2X_7$ receptor pore [36, 38–41]. The oligodendroglial cell death is responsible for systemic damage of white matter observed in periventricular leucomalacia [42] or in Binswanger's disease [43].

Neuroglia also emerges as a key player in chronic neurological diseases. Significant remodelling of astrocytic morphology and function was observed in various types of epileptiform disorders [44]. The post-mortem analysis of the epileptic brains found profound reactive astrogliosis [45, 46]. In animal models of epilepsy compromised astroglial K^+ buffering, water transport and ability to accumulate glutamate

were observed [46, 47]. Astrocytes in hippocampus of patients with temporal lobe epilepsy were found to express a specific *flip* variant of the GluR1 subunit of AMPA receptors, which mediate prolonged glutamate-induced depolarisation that in turn can produce Ca^{2+} overload and Ca^{2+} toxicity [48, 49]. The Ca^{2+} overload in epileptic astrocytes can also result from up-regulated expression of MGluR5 receptors linked to the intracellular Ca^{2+} mobilisation [50]. In autoimmune child epilepsy (Rasmussen syndrome) increased Ca^{2+} influx can reflect autoimmune-induced alterations in GluR3 AMPA receptor subunits [51]. Chronic astroglial atrophy and astroglial cell death were observed in psychiatric disorders including depression [52]. There are also indications that altered release of gliotransmitter D-serine can be involved in pathological glutamatergic transmission in schizophrenia [25, 53]. Schizophrenia is also associated with a profound atrophy of astrocytes and oligodendrocytes with aberrant myelination [54–58]. Oligodendroglial damage also assumes the central role in a variety of demyelinating disorders, including multiple sclerosis [59–61].

Microglial cells, being the innate immune and phagocytic cellular elements of the CNS, are invariably involved in every type of neuropathology. Brain insults of multiple aetiology trigger complex and multistage process of microglial activation that determines response of microglial cells to brain lesion and shape the course of neuroinflammation [22, 23]. Furthermore, the genetic factors associated with increased innate immunity and microglial activation were recently reported in patients with Parkinson disease [62].

Neuroglia in Neurodegeneration: Astroglial Atrophy and Astrogliosis

For many years, neurodegenerative diseases were considered to be a specific pathology of neurones. Recent years, however, have challenged the neurocentric views and evidence demonstrating the pathological potential of neuroglia began to accumulate (see [26, 27, 63–68] for review). Astroglial changes in the progression of neurodegenerative diseases are complex. It was generally believed that neurodegeneration triggers reactive astrogliosis and reactive astrocytes in turn contribute to neuroinflammation, which is considered to be an important component of neurodegenerative diseases [69]. Recent studies of various animal models of neurodegenerative diseases revealed another generalised reaction of astroglia—their atrophy [63, 70, 71]. Furthermore, it appeared that atrophic changes in astroglia occur at the early stages of neurodegenerative process, and may result in fading astroglial support that can affect synaptic transmission and may be linked to early cognitive deficits. Below, we shall overview the recent data on astroglial reactions in various forms of neurodegenerative diseases.

Immunodeficiency Virus-1 (HIV-1)-Associated Dementia (HAD) The HIV-1 exclusively infects microglial cells, whereas the latter release neurotoxic factors causing neuronal death [72]. In HAD, astrocytes undergo profound pathological changes, which are represented by both astrogliosis and astrodegeneration. The progression of HAD is associated with a significant astroglial cell loss through apoptosis in the basal ganglia. This astroglial death is particularly profound in subjects with rapidly progressing cognitive deficits [73]. At the same time significant astrogliosis is observed in the entorhinal cortex and in the hippocampus [74]. In HAD, the astrocytes contribute to neuronal toxicity through massive release of glutamate following activation of $CXCR_4$ chemokine receptors by TNF-α released by activated microglia [75].

Non-AD Dementia The early apoptotic death and dystrophic remodelling of astrocytes have been found in different forms of frontotemporal dementia such as, for example, frontotemporal lobar degeneration and Pick's disease [76]. This latter study also found a correlation between the degree of glial atrophy and the severity of dementia. These findings, however, were not universally acknowledged; post-mortem analysis of brains derived from patients with frontotemporal dementia found profound astrogliosis in the frontal and temporal cortices [77]. Similarly, prominent astrogliosis was observed in thalamic dementia; interestingly, the pathological remodelling of astrocytes was proposed to be the main pathological event in this type of dementia [78].

Wernicke Encephalopathy Dystrophic changes in astroglia were also discovered in the thiamine deficient animal model of Wernicke encephalopathy. These changes included decreased expression of GFAP, astrocytic glutamine synthetase and astrocytic GAT-3 GABA transporter. The profound neuronal loss observed in Wernicke encephalopathy is primarily associated with astroglial failure to contain extracellular glutamate levels; the key pathogenetic role belongs to down-regulation of EAAT1 and EAAT2 glutamate transporters in dystrophic astrocytes [79, 80].

Amyotrophic Lateral Sclerosis Early atrophic changes in astroglia occur in amyotrophic lateral sclerosis (ALS) animal models (hSOD1G93A transgenic mice) before neuronal death and the appearance of clinical symptoms [27, 81]. Progression of the ALS triggers reactive astrogliosis [82]; although atrophic astrocytes are also present even at the advanced stages of the disease [27, 81]. The role of astroglia in ALS progression is further supported by recent observation that silencing of ALS-related mutant SOD1 gene in astrocytes delayed the appearance of clinical symptoms in transgenic mouse model [83].

Parkinson's Disease The contribution of astroglia to pathogenesis of another major neurodegenerative disease, the Parkinson disease, remains virtually unknown. The density of astrocytes in the substantia nigra, however, is the lowest in the brain. In addition, it is well documented that astrocytes protect dopaminergic neurones in neuronal-glial co-cultures [66, 84, 85]. Incidentally, astrocytes prevent direct neurotoxicity of L-DOPA and convert L-DOPA into a trophic agent; therefore astroglia is critically important for L-DOPA substitute therapy [66, 84]. In addition, astroglial cells may support differentiation of stem cells into dopaminergic neurones and promote their incorporation into the neuronal circuitry [66]. It is conceivable to speculate, therefore, that even relatively minor astroglial atrophy in substantia nigra may facilitate the selective loss of dopaminergic neurones.

Alzheimer's Disease Alzheimer's disease (AD; [86]), which exists in both genetic (family Alzheimer's disease or FAD) and sporadic forms, is characterised by progressive neurodegeneration and cognitive decline. The AD is diagnosed based on a specific histopathological hallmarks represented by focal extracellular deposits of fibrillar β-amyloid (also called neuritic or senile plaques) in brain parenchyma and in the wall of blood vessels and intraneuronal accumulation of neurofibrillary tangles composed from abnormal hyperphosphorilated tau filaments [87–89]. The first senile plaques appear in the transentorhinal cortex; subsequently,

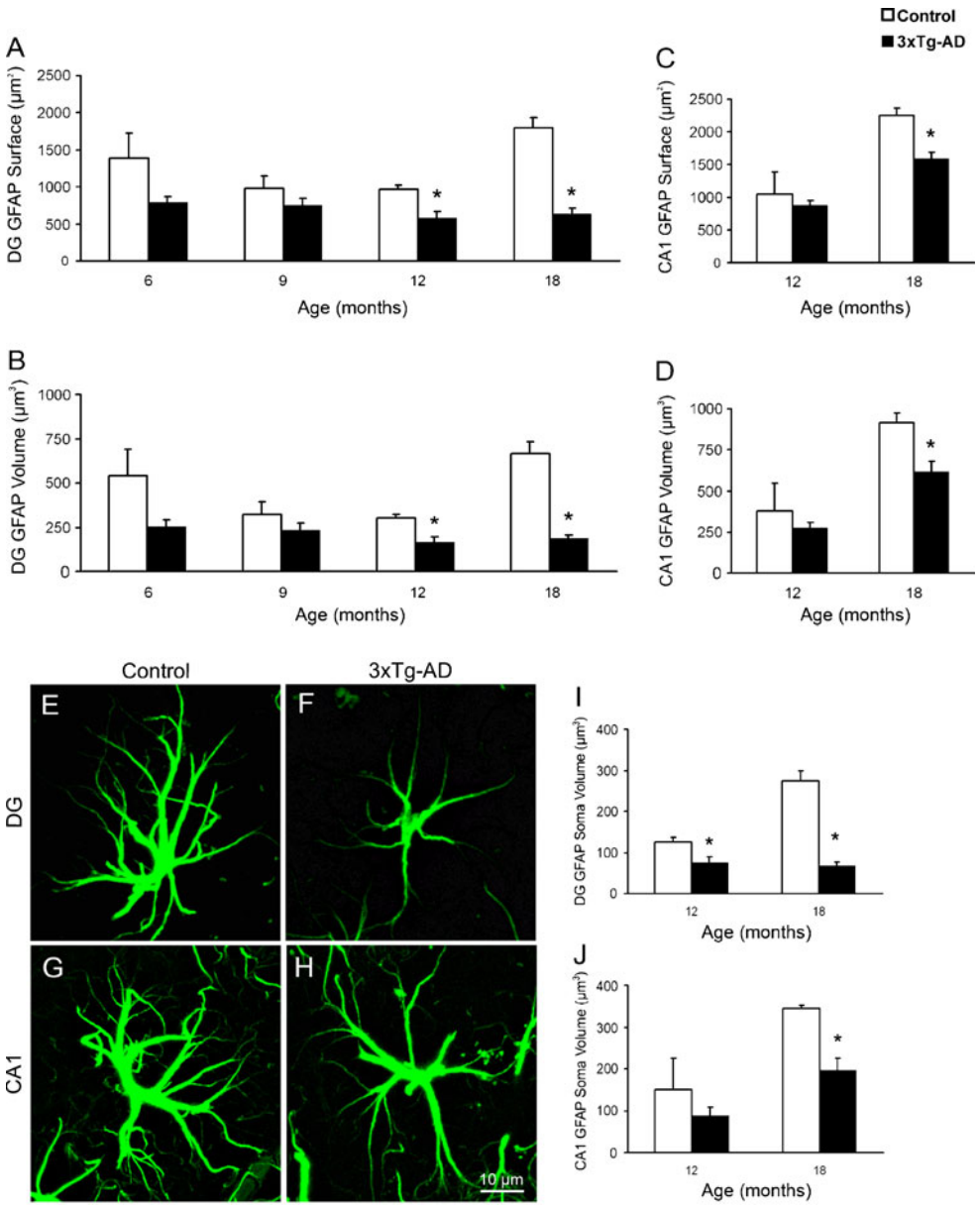

Fig. 1 Astrodegeneration in transgenic AD mice. Graphs showing GFAP surface, volume, and soma volume decrease in both the DG (**a**, **b**, **i**) and the CA1 (**c**, **d**, **j**) of the hippocampus of the 3×Tg-AD mice when compared with control animals. *Bars* represent mean ± SEM. *$p<0.05$. **g**–**j** Confocal micrographs illustrating the astrocytic atrophy in 3×Tg-AD mice in the DG (**f**) and CA1 (**h**) compared with control animals (**e** and **g**). Reproduced from [70] with permission

the pathology spreads to the entorhinal cortex and hippocampus. At the advanced stages of the disease, the neurodegeneration engulfs the temporal, frontal and parietal lobes [90, 91]; at these late stages, the grey matter undergoes severe atrophy, which is manifested clinically by profound dementia.

It is generally believed that the AD is associated with a reactive gliosis; and indeed studies of the post-mortem

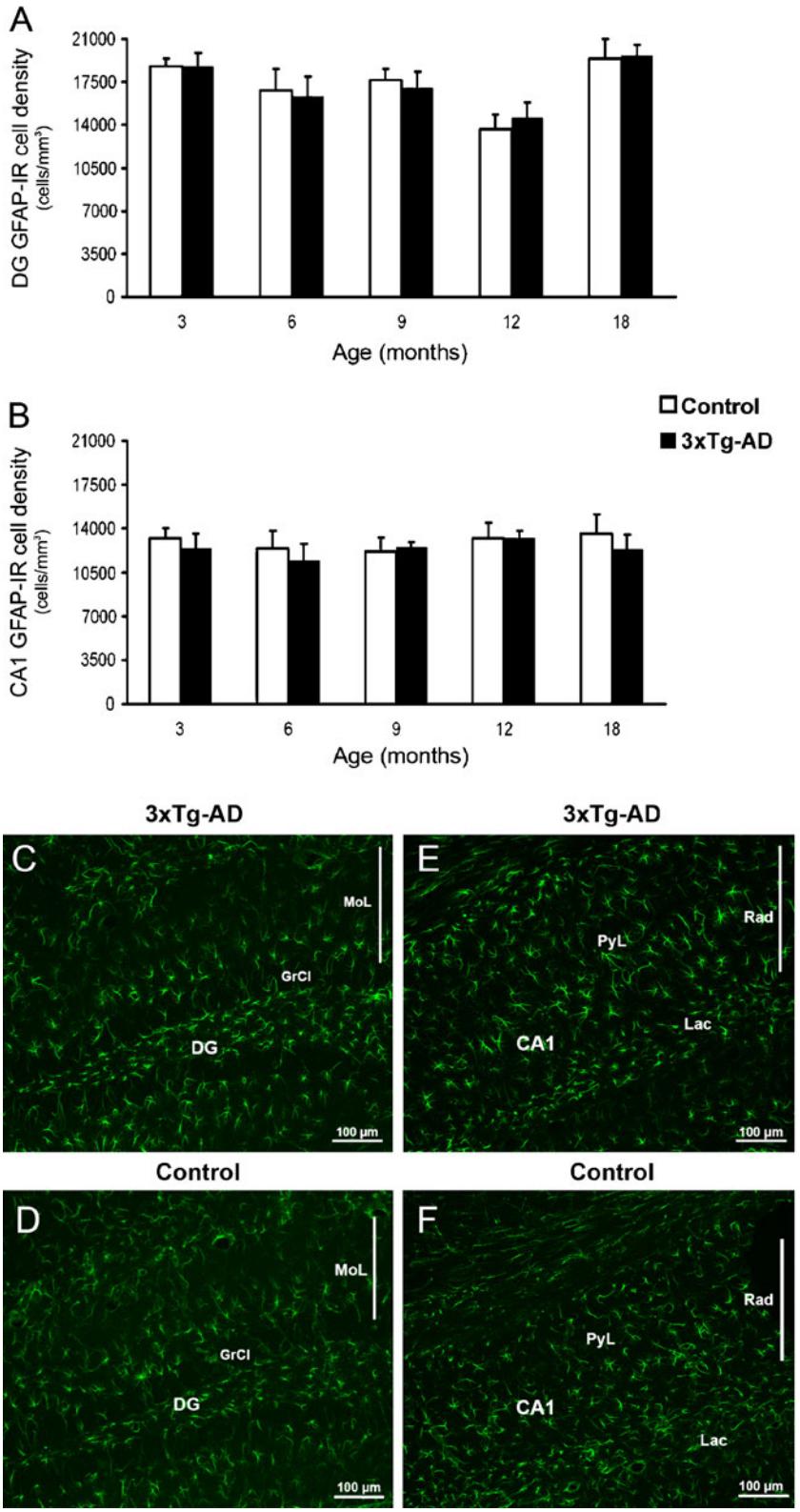

Fig. 2 Astroglial density remains constant at all ages in transgenic AD mice. **a**, **b** Numerical density (number of cells/mm^3) of GFAP-IR cells in the **a** DG and **b** CA1 of 3×Tg-AD mice compared to control animals. *Bars* represent mean ± SEM. **c**–**f** Confocal images illustrating the expression and number of GFAP-IR cells in the DG (**c**) and CA1 (**e**) of 3×Tg-AD mice compared to non-Tg animals (**d**, and **f**, respectively). *DG* dentate gyrus, *GrCL* granule cell layer, *Mol* molecular layer, *PyL* pyramidal layer, *Rad* stratum radiatum, *Lac* stratum lacunosum moleculare. Reproduced from [70] with permission

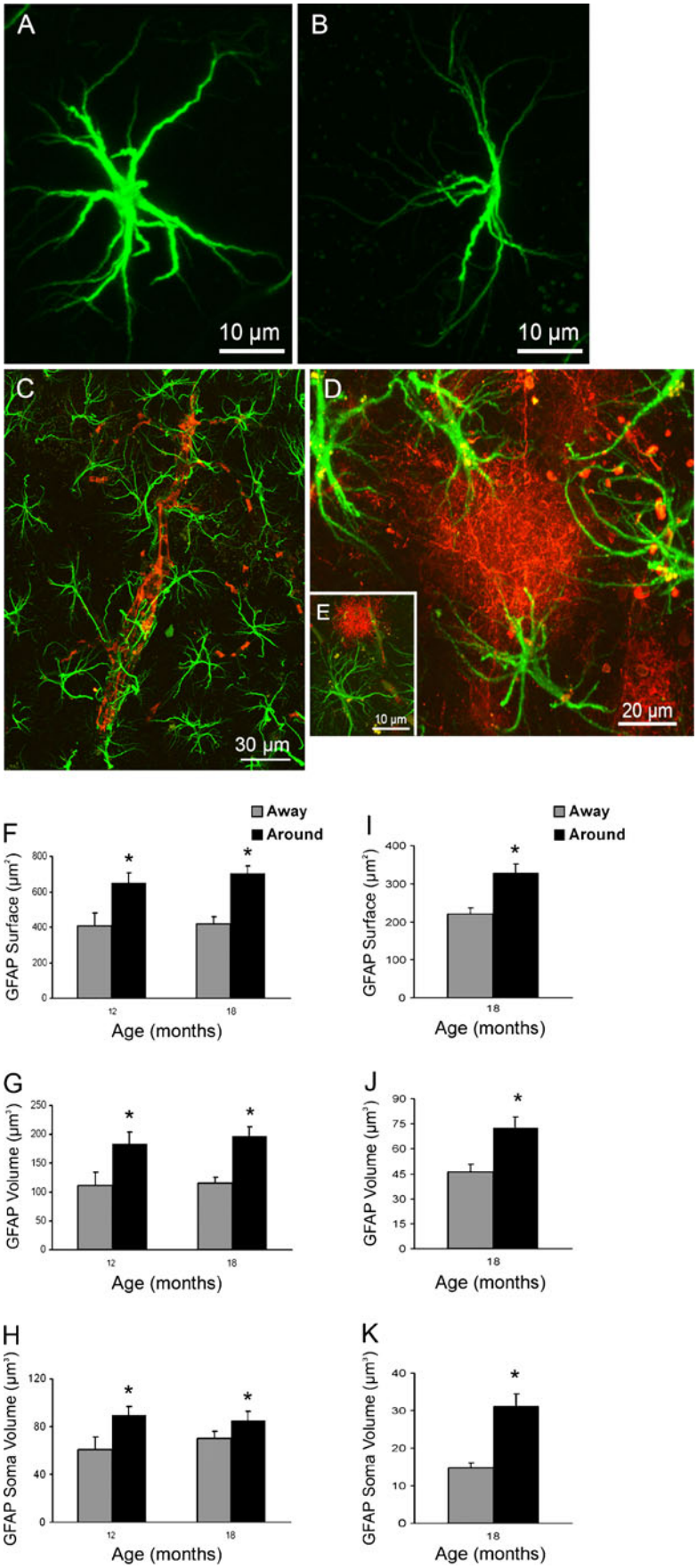

Fig. 3 Concomitant astroglial atrophy and astrolgiosis in trasngenic AD animals. **a**, **b** Confocal images of hippocampal preparations labelled by GFAP illustrating differential changes in GFAP profiles in astrocytes associated with the Aβ plaques (**b**) and distant to the plaques (**b**). **c**–**e** Dual labelling images (GFAP in *green* and Aβ in *red*) in 3×Tg-AD mice showing the accumulation of astrocytes around the Aβ plaques and vascular Aβ deposits. Astrocytes surrounding Aβ plaques (**b**, **e**) and Aβ-loaded blood vessel (**c**), undergo astrogliosis. **f**–**k** Bar graphs showing GFAP positive astrocytic surface (**f**), volume (**g**) and soma volume (**h**) differences between astrocytes located around the amyloid plaques (Aβ) and those distant to the plaques in the CA1 of 3×Tg-AD animals. **i**–**k** Similar astrocytic surface (**i**), volume (**j**) and soma volume (**k**) differences are observed in the DG at 18 months of age. *Bars* represent mean ± SEM; *$p<0.05$. Modified from [70] with permission

tissues demonstrated prominent reactive astrogliosis, inclusion of astrocytes into senile plaques and activation of microglia [26, 63, 69, 92]. Incidentally, the first observations of astrocytes being a morphological component of the senile plaque were made by Alois Alzheimer already in 1910 [93]. Reactive astrogliosis in AD can be triggered by extracellular accumulation of β-amyloid peptide (Aβ); both aggregated β-amyloid and amyloid plaques isolated from human AD brains induced astrogliotic reactions in vitro [94]. Exposure of cultured astrocytes to Aβ also triggered astroglial Ca^{2+} oscillations, which were linked to neurotoxicity in neuronal–astroglial co-cultures [95, 96]. Abnormal astroglial Ca^{2+} oscillations were also observed in vivo, in mice expressing mutant human Aβ precursor protein (APP) and mutant presenilin 1 (PS1; APPswe:PS1ΔE9) in neurones. In this model, characterised with early appearance of amyloid depositions, astrocytes closely associated with plaques demonstrated spontaneous long-distance propagating Ca^{2+} waves [97].

At the same time, the longitudinal morphological studies performed on the triple transgenic AD mice (3×TG-AD) demonstrated that astrocytes undergo complex age-dependent morphological changes (Fig. 1, [63, 70]). The 3×TG-AD mice harbour mutant genes for amyloid precursor protein (APP_{Swe}), for presenilin 1 $PS1_{M146V}$ and for tau_{P301L} [98, 99]. At the early (i.e. pre-plaque) stages of the AD, astrocytes in hippocampus and entorhinal cortex (from 6 months and 1 month of age, respectively) demonstrate signs of atrophy ([63, 70], and author's own observations; Fig. 2). These atrophic changes were manifested by reduced expression of GFAP (surface and volume coverage), decreased volume of cell somatas and decreased number and degree of branching of cell processes (Fig. 2) [63, 70]. At the same time, the overall number of astrocytes in hippocampi and entorhinal cortex of AD animals did not change with age.

At the advanced ages (12 and 18 months) when the brain parenchyma is infested with senile plaques, clear signs of reactive astrogliosis become evident. Numerous hypertrophic astrocytes were specifically associated with senile plaques and β-amyloid infested blood vessels [63, 70] (Fig. 3). This hypertrophy is characterised by an increased (up to 70%) volume and surface of both astrocyte somatas and processes (Fig. 3).

The early atrophy of astroglial cells may have important pathological consequences. Decrease in astroglial domains may reduce synaptic coverage, alter neuronal metabolic support and functional performance of neuro-vascular units and increase neuronal vulnerability to neurotoxic attack.

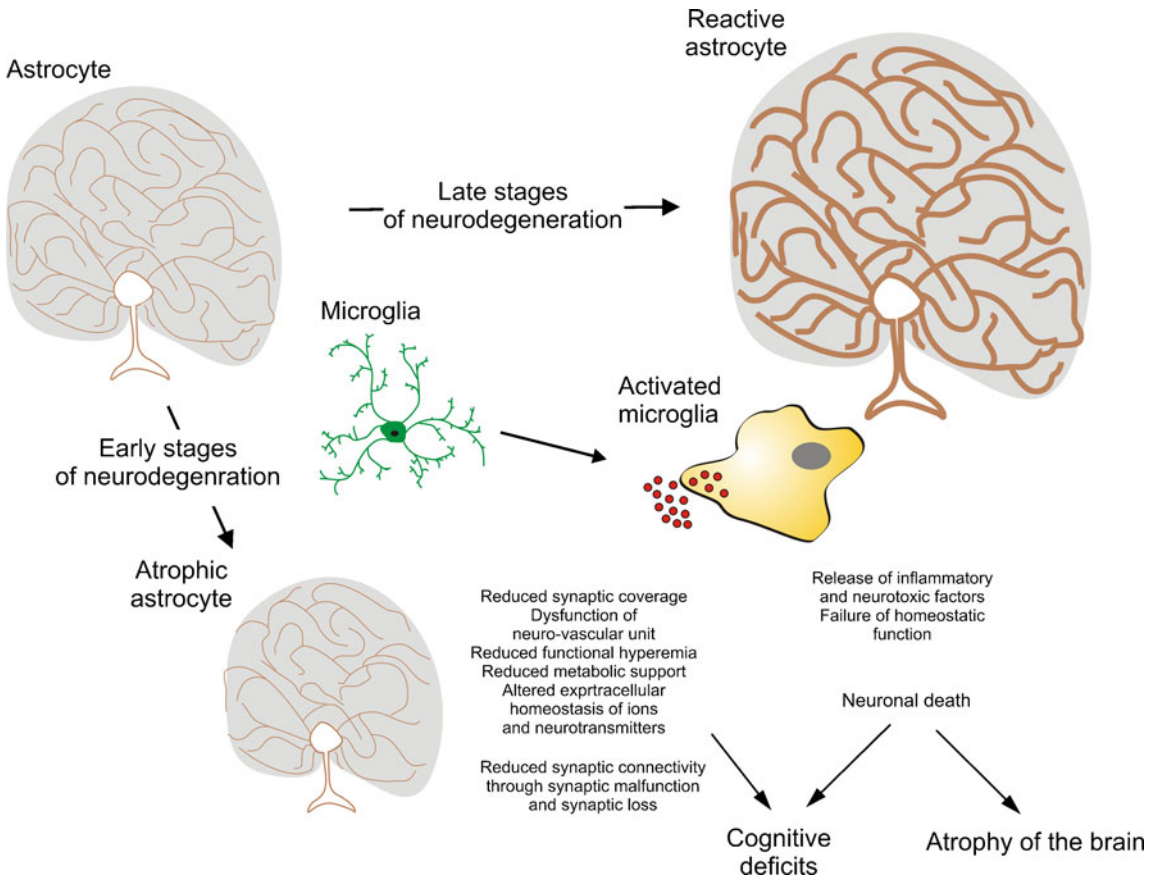

Fig. 4 General scheme of possible role of neuroglia in neurodegeneration. See text for further details

This early astroglial atrophy can therefore lead to synaptic malfunction, decreased synaptic strength and altered synaptic plasticity with obvious cognitive consequences.

Conclusions

Neuroglial cells are fundamental for the progression of neurodegenerative process. At the early stages of various types of neurodegenerative diseases astroglial cells undergo atrophic changes. These changes may affect synaptic connectivity, being thus responsible for early cognitive deficits and reduce neuroprotective potential of glial cells thus increasing the vulnerability of neurones to different types of neurotoxic insults. At the later stages, neurodegenerative process triggers astrogliosis and activation of microglia, which both contribute to neuroinflammatory component of neurodegenerative diseases (Fig. 4).

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