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Astroglia in Alzheimer's Disease

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Abstract

Alzheimer's disease is the most common cause of dementia. Cellular changes in the brains of the patients suffering from Alzheimer's disease occur well in advance of the clinical symptoms. At the cellular level, the most dramatic is a demise of neurones. As astroglial cells carry out homeostatic functions of the brain, it is certain that these cells are at least in part a cause of Alzheimer's disease. Historically, Alois Alzheimer himself has recognised this at the dawn of the disease description. However, the role of astroglia in this disease has been understudied. In this chapter, we summarise the various aspects of glial contribution to this disease and outline the potential of using these cells in prevention (exercise and environmental enrichment) and intervention of this devastating disease.

Keywords

Pathological ageing; Astrocytes; Alzheimer's disease; Astroglial atrophy; Neurodegeneration; Calcium signaling; Stem cells

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11.1 Senile Dementia—The Outcome of Pathological Ageing

Dementia as a medical term was introduced in the first century AD by Aulus Cornelius Celsus in his fundamental discourse *De Medicina* [50] to characterise major cognitive impairments of the mankind. The term dementia originates from the prefix “de” (meaning “out of”), the stem “ment” (‘mind’) and the suffix “ia” (diseased condition). Historically, this term was used in a very broad sense to indicate chronic cognitive impairments associated with psychotic symptoms such as delusions or hallucinations. However, dementia was not associated with age-dependent cognitive decline, although from the very dawn of medical observations, these impairments were considered as an essential and inevitable part of ageing process. Already in the seventh century BC, Pythagoras defined the advanced ages of human life as “senium” when “the system returns to the imbecility of the first epoch of infancy” [26]. From Aristotle to Lucretius and Galen, the ageing was considered to be associated with mental decline, impossible to arrest or recuperate [26, 38, 121, 302]. This gloomy outlook was not, however, shared by Cicero who believed in selective development of a senescence-dependent cognitive decline: “senile imbecility does not occur in all old men, but only in those of feeble mind” [54].

Over centuries the mental weakness of old people was defined as senility, idiocy, morosis, dotage, etc.; in 1794, the term dementia was formalised by Philippe Pinel and this term was officially recognised by the French Law [291]. At the end of the nineteenth century, the definition of senile dementia became widespread and underlying histopathology became to be scrutinised. The specific lesions, the plaques (then known as *miliary foci*), were discovered by Block and Marinesco in the brain of old epileptic patient [36], and subsequently these plaques were observed in the post-mortem tissues of patients suffering from senile dementia by Redlich and by Otto Fischer [77, 225]. In 1903, Max Bielschowsky developed an improved version of the Golgi silver stain that allowed visualisation of neurofibrilles [30]. Using this new technique, Alois Alzheimer (in 1906) was able to visualise neurofibrillary tangles in the post-mortem brain of Mrs. Augusta D, whom he first seen in 1901 in Frankfurt with the symptoms of confusion, delusions and dementia. These tangles displayed extraordinary thickness and often merged into dense bundles reaching the surface of a neurone [7, 26]. The brain of Augusta D also contained senile plaques, and thus the case of early dementia associated with appearance of senile plaques and pathological neurofibrillary tangles has been reported in 1907 [7]. This was a rather unique description, which differed from the widespread dementia of the early twentieth century associated predominantly with neurosyphilis or vascular ischemic brain damage. The disease was named “Alzheimersche krankheit” by Emil Kraepelin in the 8th edition of his immensely influential textbook on Psychiatry (*Psychiatrie: Ein Lehrbuch fuer Studierende und Arzte*). Kraepelin defined this new disease as a rapidly progressive, early-onset dementia distinct from the senile dementia [136]; for the history, people involved, histological details and controversies see [27, 109, 172].

Alzheimer’s disease (AD) was rarely diagnosed in the first half of the twentieth century and was generally regarded as a rare pathology that affected relatively young persons. Only in 1960, the AD histopathology was related to the sporadic cases of age-dependent (i.e. senile)

dementia and the notion of AD as senescent-associated pathology had been developed [244, 245, 290]. It seems also that the pandemic of the senile dementia observed in recent years has evolved over the last century. Detailed physiological investigation of organs and systems of an extended population (826 subjects) of elderly (80–100 years of age) inhabitants of the UK performed in 1889 revealed surprisingly little changes in their cognitive status. Furthermore "… the brain in many held out as well or better than other organs - which may be regarded one of the bright rays, if not the brightest, in the centenarian landscape" [111]. Indeed, in this study dementia was observed only in 2 out of 74 centenarians. This contrasts remarkably with our times, when >50% of people older than 85 demonstrate signs of severe cognitive impairment [343]. Of course, evolution of epidemiological changes may be interpreted from many angles, and yet it is impossible not to speculate that an increased environmental toxicity, changes in diet and mounting social pressure have contributed to a rise of sporadic AD in the modern population.

Increased prevalence of senile dementia at advanced age parallels increase in life expectancy. Modern definition regards AD as a severe neurodegenerative disorder associated with specific histopathological markers represented by (i) focal extracellular deposits of fibrillar β-amyloid generally known as neuritic or senile plaques in the brain parenchyma and the walls of blood vessels, and (ii) intraneuronal accumulation of neurofibrillary tangles composed of abnormal hyperphosphorylated tau filaments [39, 70]. AD affects specific brain regions associated with learning and memory, including the basal forebrain, the hippocampus and the neocortex. Clinical symptoms of AD are manifested by a progressive decline of cognitive functions including short- and long-term memory [185]. At advanced stages of the disease, clinical presentation of AD is complicated by a variety of behavioural disturbances including agitation, irritability, anxiety, delusions and depression [165].

Conceptually, two forms of AD are defined: (i) early-onset or familial Alzheimer's disease (FAD) and (ii) late-onset or sporadic AD, or SAD [35]. Epidemiologically, the late-onset SAD accounts for the absolute majority (95–99%) of AD cases in people above 65 years of age. The familial variant of AD is associated with mutations in three genes encoding for amyloid precursor protein (APP), presenilin-1 (PS-1) and presenilin-2 (PS-2), which are inherited in an autosomal dominant manner [23, 257, 294]. In contrast to SAD, which is linked to an old age, the familial AD occurs in much younger group of patients between 40 and 50 years old; the FAD is characterised by a rapid progression and idiosyncratic clinical manifestation. Anatomical and histopathological progression of AD begins from early degeneration of cholinergic neurones in the nucleus basalis of Meynert and septum. In parallel, the accumulation of intraneuronal β-amyloid and formation of neurofibrillary tangles develop, which ultimately leads to an emergence of senile plaques [182]. Deterioration of neuronal networks begins with synaptic damage and malfunction which affects CNS plasticity; these changes occur prior to the formation of senile plaques and neurofibrillary tangles and prior to neuronal death [251, 255]. In addition, this process suppresses neurogenesis, which further impairs neuronal plasticity [231, 237]. Apart from the cholinergic system, AD pathology impairs other major neurotransmitter systems including noradrenergic, serotonergic and dopaminergic [153, 234, 348].

11.2 Experimental Animal Models of Alzheimer's Disease

Alzheimer's disease, similar to other neurodegenerative diseases, is a specific disease of humans; animals as a rule do not develop AD-like pathology [289]. Experimental study of AD therefore requires the development of animal disease models which are capable of faithful reproduction of single or multiple subsets of neuropathological, histological, cellular, behavioural or biochemical alterations resembling those seen in classical AD [48, 91].

11.2.1 Old Animals

The very first models of AD were represented by aged animals [28, 29, 289]; several species from rodents to primates have demonstrated atrophy and death of basal forebrain neurones expressing choline acetyltransferase or nerve growth factor [60, 78, 248]. In monkeys, alterations of cholinergic neurones were even associated with β-amyloid depositions [289]. In addition, old animals showed not only a cholinergic dysfunction but also a concomitant alteration of other neurotransmitter systems such as the monoaminergic, peptidergic or serotonergic [15, 176, 198, 234].

11.2.2 Lesions

The global lesion models of AD (Table 11.1) relied on destruction of certain brain areas. At the beginning, the electrolytic lesions were used; these caused diffuse damage of several brain areas and lacked specificity [156, 289]. In the majority of global lesion models, the non-selective excitotoxic toxins such as NMDA, ibotenic acid, quisqualic acid, quinolinic acid, colchicine and other alkaloid substances were employed [289]. Injections of these substances triggered cell death with consequent neurological dysfunctions including impaired cognition. The global lesion models also employed injections of alcohol, which is toxic to cholinergic neurons [13, 289]; or injections of β-amyloid peptides, which produces multiple alterations of corticobasal neurones affecting acetylcholine release and cholinergic receptors [88, 211].

As mentioned above, a loss of cholinergic neurones is a prominent feature of AD [18]. With this in mind, animal models, which employed specific lesioning of cholinergic neurones, were developed. Among these, the most relevant were the rodent models with lesions in the nucleus basalis magnocellularis, which is the equivalent of the nucleus of Meynert in humans [214, 322], in the diagonal band of Broca and the septum [289] (Table 11.1).

Specific cholinergic lesion models used toxins, which affected only cholinergic neurones in the brain regions relevant to AD, including septum, nucleus basalis magnocellularis and the diagonal band of Broca, but did not impair non-cholinergic neurones [289, 325]. For example, the AF64A cholinotoxin, which binds to the high-affinity choline uptake system, was injected. Alternatively, the immunotoxin 192 IgG-saporin that binds selectively and irreversibly to low-affinity nerve growth factor receptor interrupting cholinergic neuronal protein synthesis was employed. Both techniques lead to selective impairment and death of cholinergic neurones [289].

Similarly, the noradrenergic system can be lesioned in rats by the injection of the construct, consisting of antibody against dopamine-β-hydroxylase, the enzyme converting dopamine to noradrenaline, and saporin [215], a ribosome-inactivating plant lectin extracted from *Saponaria officinalis* (Caryophyllaceae) [17, 151]. This technology allows a selective and gradual lesioning of noradrenergic neurones in the brain stem nucleus locus coeruleus, the primary site of noradrenaline production in the CNS [75]. Upon injection into the LC, this immunotoxin binds dopamine-β-hydroxylase, which is not only localised mainly in the cytosol, but also at the plasma membrane surface of noradrenergic neurones [271, 321]. Due to its structure, saporin cannot enter the cell [56], but when coupled to a carrier molecule (for example, an antibody), is able to specifically bind a surface antigen protein (such as dopamine-β-hydroxylase, in this case), the toxin gains access to the cytosol and binds to the ribosomal 60S subunit, interfering with protein synthesis, and soon leading to cell death [326]. In initial anatomical investigations, the immunotoxin, infused into the lateral ventricles of either adult [331] or developing rats [57], produced specific and dose-dependent depletions of locus coeruleus neurones, with no effects on other cholinergic, dopaminergic or serotonergic neuronal populations [153]. The possibility to induce a partial or total noradrenergic loss (by varying the injected dose) makes this immunotoxic approach an ideal model to study events within the noradrenergic projection system, as they occur during age-related demise of locus coeruleus in humans [329].

11.2.3 Transgenic Animals

The AD models described above, although triggering neuronal death with consequent cognitive impairments, did not mimic histopathology and temporal progression of the disease. In the last two decades, an alternative and much more effective approach of using transgenic technologies have produced numerous models of familial forms of AD, which have been widely employed in experimental research. These transgenic animal models replicate several neuropathological features of AD (Table 11.2 and [91, 142, 232]) and they are based on mutated genes isolated from patients with various forms of familial AD. The very first transgenic animal carrying mutant APP and showing an AD-like pathology was developed in 1995 [83]. In this model, known as PDAPP, several pathological hallmarks of AD have been identified, including extracellular β-amyloid deposits, dystrophy of neurites, astrogliosis and memory impairments. Memory impairments, however, did not show any correlation with β-amyloid load [83]. The next transgenic AD mouse model, designated as Tg2576 mice, harboured APP_{swe} (Swedish K670 N/M671L) mutation; this model developed numerous senile plaques in parallel with learning and memory impairments, which begun to develop from 9 months of age onwards [110]. The next generation of transgenic models carried double mutation of APP gene; such a model known as APP23 demonstrated some (~14%) neuronal death in the hippocampus [72, 272]. The next step was to combine mutated APP and PS genes; co-expression of $PS1_{dE9}$ with APP_{Swe} resulted in an AD mouse model characterised by accelerated β-amyloid deposition and memory deficits but without tangle formation [250]. These developments culminated in creation of 5xTG AD mice, designated as Tg6799; these animals carry a single human APP Swedish K670N/M671L double mutation as well as the Florida I716V mutation, and the London V717I mutation, along with PS with double M146L and L286V mutations. These mice develop amyloid depositions as early as 2 months of age [200].

In parallel to the animal models with increased β-amyloid production, the pathological tau models also have been created; the first being produced in 1995. In this model, the hyperphosphorylated tau was accumulated in neuronal somata and dendrites, although neurofibrillary tangles were never developed [90]. The next tauopa thy model, over-expressing Tau_{P301L}, did develop neurofibrillary tangles without β-amyloid pathology and neuronal loss [159].

In 2003, the triple transgenic AD mice (3xTg-AD) was created combining the mutants of the three major implicated genes; these animals harbour the mutant genes for APP_{Swe}, for presenilin PS1M146V and for Tau_{P301L} [201, 202]. These animals demonstrated temporal- and region-specific Aβ and tau pathology, which resembles that seen in the human AD brain. Additionally, the 3xTg-AD animals also displayed plaques and tangles, and also showed reduced long-term potentiation in the hippocampus along with functional and cognitive impairments seen as deficient spatial and long-term memory [201, 202]. These pathological changes progress in an age-related manner; most importantly functional deficits precede the appearance of histological hallmarks. Cognitive deficits in the 3xTg-AD model correlate with the accumulation of intraneuronal Aβ [44, 177]. Moreover, at the cellular level, changes in astroglial subcellular vesicle traffic contribute to the pathophysiology of AD [268, 269].

11.3 Neurodegenerative Diseases and Neuroglia

Neurodegenerative diseases, which affect almost exclusively humans, are chronic disorders that result in a progressive loss of function, structure and number of neural cells, ultimately resulting in atrophy of the brain and profound cognitive deficit. The aetiology of neurodegeneration is complex and multifaceted. Neurodegeneration can have a genetic background or it can be instigated by acute trauma, by chemical poisoning, by metabolic insufficiencies or by infectious attacks, as well as by vascular abnormalities, or by sporadic accumulation of genetic/biochemical errors of unknown nature. At the early stages, neurodegeneration as a rule affects synaptic contacts in the brain tissue, thus causing early cognitive deficits. The early stages of neurodegeneration are of course of specific significance, because during this early phase the pathological process can be arrested or even reversed, thus offering the hope for preventing the cognitive decline.

Cellular and molecular mechanisms of underlying initiation and progression of neurodegenerative diseases are highly complex, which makes it almost impossible to identify a single leading cause. At the level of cellular biochemistry, neurodegeneration is frequently linked to aberrant handling of proteins, which promotes intra- or extracellular accumulation of abnormal proteins such as, for example, β-amyloid, tau or α-synuclein [116]. At a more systemic level, however, neurodegeneration reflects a generalised failure of brain homeostasis, which results in a functional and structural decline in the connectivity of neural networks, thus ultimately destroying information processing. Neurodegeneration starts from functional impairment of synaptic connectivity and synaptic plasticity which leads to a neurotransmission misbalance; these processes stipulate early cognitive deficiency. With further progression of the neurodegenerative process, the structural abnormalities develop, trigger disappearance of synapses and death of neural cells, ultimately resulting in a

generalised atrophy of the brain accompanied with profound cognitive deficiency [133, 207, 254, 282].

The neuroglia provides for the birth, maintenance and demise of synapses, as well as for overall homeostasis of the nerve tissue, these functions being summarised in a concept of the astroglial cradle [303, 304]. Thus, these non-neuronal cells likely represent the main cellular element shaping the progression of neurodegenerative processes. The generally acknowledged and prevailing point of view considers neurones as main substrates of neurodegeneration, and it is generally assumed that failures in neuronal protein synthesis and/or direct neuronal damage caused by various factors constitute the leading mechanism of neurodegenerative pathologies. These neurone-centric doctrine has been challenged in the past decade, with considerable attention re-routed to neuroglia, which being primary cells responsible for the brain homeostasis and defences, fundamentally contribute to an overall homeostatic failure promoting neurodegeneration [40, 45, 106, 212, 235, 238, 242, 300, 307, 310, 311, 315].

11.4 Astroglial Atrophy and Astrogliosis in Neurodegenerative Diseases

Astrogliopathology in neurodegenerative diseases includes reactivity and astroglial atrophy, asthenia and loss of function. These processes develop in a stage-specific manner and contribute to pathological progression; frequently astroglial asthenia develops at early stages of the disease, whereas at the advanced stages an emergence of disease-specific lesions (for example, senile plaques) and death of neurones instigates astroglial reactivity [14, 306, 308, 317]. Pathological changes in astroglia evolve in parallel with microglial responses. Microglial reactions, at least in the context of human disease, are represented by either activation (that may contribute to neuroinflammatory progression) or microglial paralysis with loss of neuroprotective capabilities, which all contribute to brain atrophy. Cells of oligodendroglial lineage are also affected, which leads to a failure in myelination and atrophy of brain connectome.

11.4.1 Neurodegeneration Following Toxic Brain Injury

Astrocytes play the leading role in chronic neurodegeneration following the brain poisoning by toxic agents. The core mechanism underlying this astroglial-dependent neurotoxicity, which leads to a substantial neuronal death, is linked to a failure of astroglial glutamate uptake. Glutamate clearance from the extracellular space is mainly accomplished by astroglial Na^+-dependent plasmalemmal glutamate transporters; astrocytes specifically express two types of these glutamate transporters, the excitatory amino acid transporters 1 and 2 (EAAT1 and 2). This glutamate uptake is fundamental for astroglia-mediated neuroprotection against glutamate excitotoxicity; suppressing of astroglial glutamate uptake greatly increases neuronal damage following exposure to glutamate [58]. Astroglial glutamate uptake is usually impaired in neurodegeneration and can be considered as one of the common mechanisms of this process [126].

Exposure to heavy metals triggers neuronal death underlying condition known as heavy metal toxic encephalopathy, which manifests itself by impaired cognition and psychotic symptoms. This neurotoxicity results from astroglial homeostatic failure; heavy metals are

accumulated by astroglial cells, thus damaging pathways responsible for glutamate homeostasis and catabolism. In methylmercury-induced encephalopathy known as Minamata disease (the name derives from the Japanese city of Minamata where massive poisoning with methylmercury occurred in 1950s, see [174]). When in astrocytes, methylmercury inhibits glutamate, glutamine and cystine transporters which compromises glutamate homoeostasis [194, 339]. Resulting increase in extracellular glutamate concentration triggers neuronal death underlying clinical symptoms that include cognitive decline, impaired vision and hearing, as well as motor symptoms. Similarly, astrocytes, endowed with capacity manganese transport system, emerge as a main target for manganese toxicity. Again, increased manganese in astroglial cells suppresses astroglial glutamate uptake with subsequent excitotoxic neuronal damage [260]. Similarly, astrocytes appear as a primary target for other heavy metals, such as arsenic, lead and cadmium, which all reduce expression of glial fibrillary acidic protein (GFAP) and trigger astroglial apoptosis, thus reducing astroglial homeostatic presence [223]. In aluminium toxic encephalopathy (symptoms of which include cognitive deficits and speech alterations), astrocytes are again the main targets. Aluminium accumulated by astrocytes impairs plasmalemmal glutamate transporters as well as gap junctions and causes astrocytic death [275]. Likewise, astroglial loss through apoptotic death plays a leading role in the enchephalotoxic damage caused by cypermethrin, a synthetic II pyrethroid insecticide [173].

11.4.2 Wernicke Encephalopathy

Wernicke encephalopathy is a pathoanatomical substrate for Korsakoff syndrome, symptoms of which include ante- and retrograde amnesia, apathy and confabulation [135, 323]. This type of encephalopathy is essentially rapidly progressing malignant thalamo-cortical neurodegeneration. The pathological mechanism of Korsakoff–W-ernicke syndrome is primarily associated with acute failure in astroglial glutamate uptake resulting from ~60 to 70% decrease in expression of EAAT1 and EAAT2 glutamate transporters. This remarkable decrease in plasmalemmal glutamate transporters expression has been identified in post-mortem human samples, as well as in the rat thiamine deficiency model of the disease [104, 105]. In addition to decrease in EAAT1/2 expression, astrocytes demonstrated signs of atrophy including decrease in GFAP morphological profiles, as well as decrease in expression of glutamine synthetase (GS) and GAT-3 GABA transporter.

11.4.3 The Human Immunodeficiency Virus-1 (HIV-1)-Associated Dementia (HAD)

In the nervous system, the HIV-1 virus primarily infects and propagates in microglial cells. Microglia contributes to neuronal death by releasing various neurotoxic factors [123, 171], including Nef protein [267]. In HAD, astroglial cells develop both astrodegeneration and reactive astrogliosis. In the basal ganglia, astrocytes undergo a serious loss with the degree of astroglial death correlated with the degree of cognitive impairments [283]. In the entorhinal cortex and in the hippocampus, astrocytes show prominent reactivity [295].

11.4.4 Non-AD Dementia

The non-AD dementia is represented by many disorders including fronto-temporal lobar degeneration, Pick’s disease, Cockayne syndrome, juvenile neuronal ceroid lipofuscinosis (JNCL) or Niemann-Pick type C disease. Astroglial contribution to these disorders is

complex with signs for astroglial atrophy and astroglial apoptotic death [42, 320] as well as for astroglial reactivity, which is particularly prominent in the frontal and temporal cortices of patients with fronto-temporal dementia [124]. In thalamic dementia, a profound astrogliosis likely represents a key pathophysiological factor [221]. There is evidence indicating uncoupling of astroglial syncytium and aberrant activity of astroglial connexin hemichannels in JNCL [43], whereas early astroglial reactivation was reported in animal models of Niemann-Pick type C disease [222].

11.4.5 Amyotrophic Lateral Sclerosis (ALS)

Astrocytes play fundamental role in the pathogenesis of hereditary familial ALS associated with the mutation of the human superoxide dismutase 1 (hSOD1) gene. In hSOD1/G93A, associated animal models of ALS astrocytes undergo atrophy, pathological remodelling loss of function and cell death. These astroglial changes precede neuronal abnormalities and the emergence of clinical symptoms [241, 242]. The key pathogenetic factor linked to the neurotoxicity is represented by deficient astroglial glutamate uptake. Selective silencing of *hSOD1* gene in astrocytes in animal model delays ALS progression [337].

11.4.6 Parkinson's Disease

The role of neuroglia in emergence and progression of Parkinson's disease remains to be fully elucidated. There are some indications for microglial activation in relevant brain regions; this activation being possibly linked to neurotoxicity [63]. This microglial response, however, can be secondary, being triggered by neuronal death [108]. In 6-hydroxydopamine (6-OHDA) animal model of Parkinson's disease, inhibition of microglial activation was found to be neuroprotective [152]. Astrocytes have been considered to provide neuroprotection to dopaminergic neurones, based on in vitro experiments [180, 181]. In primary neuronal–glial co-cultures, astrocytes were shown to convert L-DOPA, the immediate precursor of dopamine, from neurotoxic to neurotrophic substance, and hence astroglia can be crucial for L-DOPA substitute therapy [179].

11.5 Astrocytes in Alzheimer's Disease

Alzheimer's disease is characterised by progressive neurodegeneration and an occurrence of specific histopathological markers represented by (i) focal extracellular deposits of fibrillar β-amyloid (also called neuritic or senile plaques) in the brain parenchyma and in the walls of blood vessels, and by (ii) intraneuronal accumulation of neurofibrillary tangles composed from abnormal hyperphosphorylated tau filaments. The initial neurodegenerative events in AD appear in the transentorhinal cortex, which subsequently spread to the entorhinal cortex and hippocampus. At later stages of the disease, the neurodegenerative process disseminates through the temporal, frontal, and parietal lobes [284, 285]. At these late stages, the grey matter undergoes severe damage with a profound loss of neurones and synaptic contacts and generalised atrophy of the brain parenchyma; this atrophy includes both white and grey matters. Contribution of neuroglia to the histopathology of Alzheimer's disease has been initially suggested by Alois Alzheimer himself; Fig. 11.1 shows original drawings of Alzheimer depicting pathologically modified glial cells of a senile plaque [8]. The role of astrocytes in the pathogenesis and progression of AD remains to be fully characterised,

primarily because of the lack of longitudinal studies assessing the status of astroglia at different stages of the disease. From analyses of human post-mortem tissues, there has been generally agreed that at the late stages of the disease there are prominent reactive astrogliosis and inclusion of astrocytes into senile plaques [106, 193, 235].

11.5.1 Astrocytes and β-Amyloid

The prevailing views on AD pathogenesis associate disease evolution with progressive accumulation of β-amyloid protein in the brain parenchyma and formation of senile plaques [87, 100, 122, 134]. Recently, however, the β-amyloid hypothesis became the subject of extensive criticism [49, 98, 99, 226]. Production of β-amyloid is mostly associated with neurones although there are several reports indicating the role of astrocytes in this process through either direct β-amyloid production or through deficient clearance.

Astroglial contribution to the clearance and degradation of β-amyloid has been suggested some 15 years ago [96, 195]. Reactive astrocytes associated with senile plaques in the transgenic AD mouse model expressing mutant APP were found to express a zinc-dependent metalloendopeptidase neprilysin, an enzyme capable of degrading β-amyloid [11]. In experiments in vitro, cultured astroglial cells obtained from healthy mice were shown to accumulate exogenous β-amyloid. In contrast, this ability was absent in astrocytes isolated from the brains of APP AD model [333]. Similarly, astroglial β-amyloid accumulation was detected in cells from the entorhinal cortex of AD patients [192]. Conversely, β-amyloid was almost never detected in astrocytes from 3xTg-AD mice (Fig. 11.1d, [203]).

Astroglial contribution to β-amyloid production is not fully characterised. Neurones, which express β-amyloid producing enzymes β- and γ-secretases, were for a long time considered to be the main source for β-amyloid [143]. Indeed, healthy astrocytes seem not to express β-secretase; nonetheless, its expression can be induced by conditions of chronic stress or neuroinflammatory environment, thus adding astroglia to amyloidogenesis [33, 82, 117, 157, 205, 243, 342]. Expression of β-secretase was detected in reactive astrocytes emerging following immune lesion of cholinergic septohippocampal afferents or an occlusion of the middle cerebral artery [243]. Similarly, expression of β-secretase was found in reactive astrocytes in AD mice models expressing mutant human APP; these models, for example, included Tg2576, K670N-M671L APP or APP V717I mutations [101, 107, 243]. Of note, an increase in production of APP was characterised in a rat model of chronic neocortical astrogliosis, induced by grafting a foetal cortical tissue in the midbrain of neonatal animals; these chronically activated astrocytes were immunopositive for APP, as well as for another AD-related marker apolipoprotein E4 [166].

11.5.2 Astrogliosis in AD

Astroglial reactivity, generally characterised by an increase in expressions of GFAP, vimentin or s100β protein, has been detected in post-mortem tissues from AD patients [19, 92, 178, 189]. No obvious correlation between GFAP levels, degree of astrogliosis and β-amyloid load was detected [261]. Similarly, no differences in GFAP expression were found between the brains obtained from cognitively sound and demented patients [324]. Reactive, hypertrophic astrocytes, associated with senile plaques and perivascular β-amyloid deposits,

are also observed in the brains of AD mice models (Fig. 11.1, [204, 235, 306]). It is important to highlight that astrogliosis in AD is never associated with the scar formation and it does not hamper the physiological non-overlap of astroglial territorial domains. It can be classified therefore as isomorphic or mild astrogliotic response. In the context of AD, the astrogliotic response can be triggered by various molecules, such as β-amyloid, molecules released from damaged cells or certain cytokines and chemokines. Soluble β-amyloid was found to initiate reactive astrogliosis in astrocytes in vitro [64]. This may be associated with certain intracellular signalling events, including, for example, Ca^{2+} signals. Such signals are indeed generated by exposure of cultured astrocytes to β-amyloid [2, 3, 94]. Treatment of cultured astrocytes with β-amyloid also resulted in inhibition of glutamate uptake, which can contribute to pathological progression [168].

11.5.3 Astroglial Atrophy in AD

Pathological changes of astrocytes in the AD pathology are not limited to astrogliotic response; it seems that astrogliosis occurs at later stages of the disease, with reactive astrocytes being mainly associated with senile plaques. Recent studies of transgenic AD mice models revealed a profound astrodegeneration that occurs at the early stages of AD progression [20, 203, 306].

Total number of astrocytes (labelled with antibodies against GFAP, s100β or GS) did not show any age-dependent variations in 3xTg-AD mice of 3–24 months of age [203, 204]. There are complex region- and disease stage-specific morphological changes in astrocytes in 3xTg-AD mice (Figs. 11.2, 11.3 and 11.4). At the early (i.e. pre-plaque) stages of the AD, astrocytes in the entorhinal cortex, prefrontal cortex and hippocampus demonstrate signs of morphological atrophy [139, 203, 204, 338]. Astroglial atrophy develops first in the entorhinal cortex (from 1 month of age, Fig. 11.2); next, it occurs in the prefrontal cortex (3–4 months of age, Fig. 11.3) and finally in the hippocampus (6–9 months of age, Fig. 11.4). Atrophy of GFAP-positive profiles preceded β-amyloid deposition and formation of senile plaques. The reduction in GFAP profiles coincided with the reduced morphological presence of astroglial cells labelled with GS antibodies in the hippocampus and in the prefrontal cortex, but not in the entorhinal cortex. Morphological atrophy of astrocytes was manifested by reduced expression of GFAP-rich cytoskeleton (surface and volume coverage) and decreased somata volume, as well as number and branching of cell processes. Very similar atrophic changes were observed in hippocampal astrocytes from another AD animal model, the mutant APP (PDAPP-J20) mice carrying the Swedish and Indiana APP human mutations [20, 21]. Astroglial atrophy was subsequently confirmed in human material, in astrocytes derived from pluripotent stem cells isolated from patients with family and sporadic AD (Fig. 11.5, [119, 184]).

At the later stages of AD pathology in hippocampi of 3xTG-AD animals (12–18 months; at this time neurofibrillary tangles also start to develop in neurones), formation of plaques and accumulation of extracellular β-amyloid initiates reactive astrogliosis. Numerous hypertrophic astrocytes accumulate exclusively around senile plaques and β-amyloid inundated blood vessels (Figs. 11.6 and 11.7; [203, 230, 316]). This astroglial hypertrophy is characterised by an increased volume and surface of both astrocyte somata and processes,

which can increase their size up to 70% (Fig. 11.3). At the same time, astrocytes positioned away from the senile plaques retain their atrophic morphology (Fig. 11.6). In contrast to the hippocampus, accu mulation of β-amyloid and formation of senile plaques do not induce reactivity of astrocytes neither in the entorhinal nor in the prefrontal cortex (Fig. 11.7, [139, 338]). Deficient reactivity of astrocytes may determine the specific vulnerability of different brain regions to AD-type pathology. Atrophy of astrocytes at the early stages of AD may have important functional consequences. The decrease in astroglial complexity may affect synaptic coverage and homoeostatic support as well as functional performance of the neuronal–glial–vascular unit. This in turn can affect connectivity in neural network, reduce synaptic strength and disturb synaptic plasticity thus contributing to cognitive deficits.

11.5.4 Loss of Astroglial Homeostatic Support Contributes to Early Cognitive Impairments

Atrophic changes in astrocytes, characterised in several AD animal models as well as in stem cells derived astrocytes appear as general diminution of astroglial territories, of astroglial coverage of neuronal membranes and overall decrease in astroglial homeostatic support. Arguably, this atrophy and loss of function of astrocytes, which occur early in the disease progression, may contribute to the disease pathophysiology. Atrophic astrocytes provide less synaptic coverage with deleterious consequences for synaptic transmission associated with compromised ion and neurotransmitter homeostasis or reduced local metabolic support; astroglial asthenia also results in decreased neuroprotection [232, 238, 316, 317]. All these changes are likely to weaken synaptic transmission and affect synaptic plasticity, thereby being responsible for initial cognitive deficiency observed at the early stages of AD.

Early cognitive deficits are the very first symptoms of AD, which start to emerge decades before the occurrence of specific histopathology [55, 282]. Loss or impairment of cognitive capacities reflects reduced synaptic connectivity due to decreased synaptic function and synaptic loss [347]. Decrease in number of synapses indeed was found to be the earliest morphological change in AD [282]; and moreover the degree of synaptic loss correlates with the severity of dementia [61, 247]. Atrophy of astroglial perisynaptic processes may indeed underlie synaptic loss at the early stages of AD. Furthermore, astrocytes are fundamental for synaptogenesis and synaptic maintenance; furthermore, astroglial plasmalemmal transporters control local concentrations of ions and neurotransmitters, most notably glutamate, that may contribute to local excitotoxicity [73, 292, 303]. Astroglial asthenia also impairs metabolic support accomplished by lactate shuttle [213]. Astrocytes are also critical for maintaining normal neurotransmission by supplying neurones with glutamine that is an indispensable precursor for both glutamate and GABA. Impairment of all these fundamental functions associated with astroglial atrophy and loss of function may be considered as a primary cause for distorted synaptic connectivity and early cognitive deficits in AD [300, 306, 316].

11.5.5 Neurovascular Unit in AD

Clinical evolution of AD is almost invariably associated with vascular deficiency and pathologies of the blood–brain barrier [276, 277]. It is well documented that the blood flow

is significantly reduced in the brains of patients with AD, with these vascular deficits being prominent already at the early stages of the disease [24, 345]. These functional deficits stem from substantial remodelling of vascularisation in the brains altered by AD pathology [74]. Brain vessels are controlled by both neuronal and astroglial inputs [112, 346]. Astrocytes are central integrating elements of neurovascular units that bridge brain parenchyma with local circulation. By secreting various agents astrocytes target pericytes, vascular smooth muscle cells and endothelial cells, thus contributing to functional hyperaemia and regulating the blood–brain barrier [191, 279, 346]. Astroglial atrophy as well as reactivity may differentially remodel the neurovascular unit, even that can occur at both early and late stages of the disease and can contribute to cognitive abnormalities and neuronal damage.

11.5.6 AD and Astroglial Metabolic Support

Metabolic deficiency of the brain is a common feature of AD. Functional brain imaging demonstrated a progressive loss of utilisation of glucose in patients with different stages of AD; deficits in brain metabolism are present already at the very early stages of the disease, having thus diagnostic significance [187, 229]. Exposure of cultured astrocytes to β-amyloid impairs cellular metabolism, although both decrease [209, 264] and increase [5] of glucose utilisation were detected. Likewise, both decrease [34, 160] and increase [31, 264] of the activity of glucose metabolism enzymes were described in post-mortem AD brains.

11.5.7 Deficient Astroglial Reactivity Defines Susceptibility of Brain Tissue to AD Pathology

Astroglial atrophy and asthenia in AD also lead to a loss of their defensive function [300]. As has been alluded previously, in experiments on 3xTg-AD mice, reactive astrocytes were accumulated around senile plaques and form perivascular β-amyloid deposits [203, 204]. These hypertrophic astrocytes are specifically associated with extracellular β-amyloid deposits, whereas astrocytes distant to the plaques remain atrophic (so in this sense astroglial atrophy emerges at the early stages of AD and is complimented by astrogliosis at later stages, when specific lesions develop). In contrast, in entorhinal and prefrontal cortices, extracellular β-amyloid accumulation does not trigger astrogliotic response (Fig. 11.7, [139, 338]) indicating failure of astroglial neuroprotection.

There are several lines of evidence demonstrating that reactive astrocytes are neuroprotective in the context of AD. For example, the Tg2576 mice (that harbour the APP_{Swe} mutation—see [110]) demonstrate early and prominent astroglial reactivity which correlates with relatively slow development of AD. Furthermore, senile plaques in these animals are resembling human β-amyloid deposit being represented by fleecy, granular, cored and diffused amyloid plaques [336], Incidentally, the Tg2576 mice display certain similarities with the prodromal stage of AD known in humans as mild cognitive impairment [16]. Astroglial capabilities to mount astrogliotic response change with age. The density of reactive astrocytes changes with age. In old Tg2576 mice, GFAP staining demonstrated prevalence of atrophic astrocytes with fewer reactive astroglial cells, which may be related with increased AD pathology in ageing [300]. Inhibition of reactive astrogliosis in the AD mouse model significantly increased β-amyloid load and exacerbated pathological progression [137].

The in vivo brain imaging of astrocytes uses PET detection of ^{11}C-deuterium-L-deprenyl (^{11}C-DED) that binds to MAO-B in the astrocytes [81]. When using a multi-tracer PET detecting ^{11}C-PIB (marker of fibrillar β-amyloid), ^{18}F-FDG (marker cerebral glucose metabolism) and ^{11}C-DED (marker of astrogliosis), the highest binding of ^{11}C-DED (which reflects maximal reactivity of astrocytes) was observed in patients with mild cognitive impairment (MCI) and high levels of fibrillar amyloid plaques in the brain (PIB+) reflecting prodromal AD [46]. Decrease in astroglial reactivity parallels the switch from MCI to full-blown AD with senile dementia again demonstrating the neuroprotective role of astrogliotic remodelling (Fig. 11.8 and [300]).

11.6 Astroglial Calcium Signalling in AD

11.6.1 Ionic Signalling as a Substrate of Astroglial Excitability

Astroglial excitability is based on spatially and temporally controlled fluctuations of intracellular concentration of ions, most notably of Ca^{2+} and Na^{+}, although recently the signalling role for K^{+} and Cl^{-} begun to be considered [130, 240, 246, 256, 313, 314, 328]. Astroglial Ca^{2+} signalling is the most studied; astroglial Ca^{2+} responses have been discovered in the late 1980s [71, 299], and are implicated in various signalling functions.

Physiological stimulation has been demonstrated to trigger Ca^{2+} signals in astrocytes in vitro, in situ and in vivo [22, 66, 129, 131, 256]. Astroglial calcium signalling has a spatio-temporal hierarchical organisation: at the cellular level, astrocytic Ca^{2+} signals are classified into local Ca^{2+} microdomains, intracellular propagating waves, global Ca^{2+} signals and Ca^{2+} oscillations [95, 196, 259, 265]. These distinct forms of Ca^{2+} signals reflect operation of different mechanisms. Global Ca^{2+} signals and propagating Ca^{2+} waves originate from Ca^{2+} release from the endoplasmic reticulum Ca^{2+} store; this release is primarily mediated by inositol 1,4,5 trisphosphate ($InsP_3$) receptor type 2, ($InsP_3R2$). Local Ca^{2+} microdomains in contrast are often generated by Ca^{2+} entry through ionotropic receptors, transient receptor potential channels, store-operated Ca^{2+} entry (SOCE) or reversed Na^{+}/Ca^{2+} exchanger [305]. Astroglial Ca^{2+} signals regulate several cellular processes, including secretion, metabolism and astroglial reactivity. Astroglial Na^{+} signalling is much less characterised, although basic parameters of Na^{+} transients evoked by physiological stimulation have been described in experiments in cultured cells and in astrocytes in brain slices [86, 127, 128, 148–150, 227, 344]. Astroglial Na^{+} signals regulate many homeostatic plasmalemmal transporters, thus coordinating neuronal activity with astroglial support [130, 240].

11.6.2 Aberrant Calcium Signalling in AD

The fundamental role of Ca^{2+} in regulation of cellular survival and cell death inspired the “calcium hypothesis of ageing and neurodegeneration” formulated by Zaven Khachatirian [125] who based this hypothesis on experimental studies of Philipp W. Landfield [146, 147]. This Ca^{2+} hypothesis posits that ageing neurones experience increased Ca^{2+} influx during depolarisation, which elevates cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$), thus triggering excitotoxicity. Subsequent studies revealed that physiological neuronal ageing is associated with much subtle alterations of neuronal Ca^{2+} extrusion, which, although capable of handling normal Ca^{2+} loads, fail to clear excessive Ca^{2+} influx. This deficit in Ca^{2+} handling

stipulates higher vulnerability of old neurones to the periods of high activity [286, 287, 312, 334]. In neurodegenerative diseases (including AD), Ca^{2+} homeostatic machinery is, however, seriously compromised, and hence these disorders have been regarded as “chronic calciumopathies” [273, 274]. Almost nothing is known about changes in Ca^{2+} homeostatic machinery, resting Ca^{2+} handling, and Ca^{2+} signalling in aged astrocytes. There are several isolated reports demonstrating a decrease in evoked astrocytic Ca^{2+} signals in mice aged 16–21 months, when compared to adult animals [144, 145].

11.6.3 Exposure to β-Amyloid Disturbs Astroglial Ca^{2+} Signalling

Whether β-amyloid is indeed a causal factor in AD or a mere epiphenomenon, exposure to it affects astroglial Ca^{2+} dynamics. Experimental studies in vitro in primary astroglial cultures demonstrated acute effects of β-amyloid on Ca^{2+} signalling. Resting $[Ca^{2+}]_i$ significantly (2–3 times) increased in astrocytes exposed to β-amyloid (in concentrations ranging between 100 nM and 5 μM) for several hours [103, 161]. These findings, however, have not been universally confirmed; several investigations found that incubations of cultured astrocytes with 100–200 nM of β-amyloid (or its toxic fragment β-amyloid25–35) for 48–72 h did not significantly change resting $[Ca^{2+}]_i$ [47, 288].

Acute exposure to β-amyloid triggered oscillations of $[Ca^{2+}]_i$ transients in cultured astrocytes and in astrocytes in organotypic slices [2–4, 52, 114, 163]. These acute effects, however, were not always observed and several studies have not noticed such acute effects [47, 288]. Treatment of cultured astrocytes with 1 μM of β-amyloid$_{1-40}$ induced $[Ca^{2+}]_i$ elevations only in 17% of all the cells, whereas application of β-amyloid25–35 triggered Ca^{2+} signals in 36% of all astrocytes [114]. In primary cultured rat newborn astrocytes, application of 1 μM of β-amyloid25–35 induced $[Ca^{2+}]_i$ transients in 27% of primary cultured rat newborn astrocytes; at 2–5 μM ~60% of astrocytes responded with $[Ca^{2+}]_i$ transients [270]. Of note, low concentrations of β-amyloid apparently stimulate astroglial Ca^{2+}-permeable α7 nicotinic cholinoreceptors, which resulted in Ca^{2+} influx and generation of Ca^{2+} responses [154, 216].

11.6.4 Pathological Ca^{2+} Signalling in AD Astrocytes In Vitro

Analysis of $[Ca^{2+}]_i$ dynamics in astrocytes isolated from several mouse models of AD also demonstrated aberrant Ca^{2+} signalling [162, 163]. Abnormally large Ca^{2+} signals have been detected in astrocytes isolated from newborn 3xTg-AD mice, indicating intrinsic alterations of Ca^{2+} homeostatic cascades [239]. Astrocytes isolated from 3xTg-AD mice in particular showed increased store-operated calcium entry (SOCE) [239]. Cultures of astrocytes isolated from 3xTg-AD animals also demonstrated aberrant kinetics of ATP-induced Ca^{2+} signals and Ca^{2+} oscillations [269]. Further analysis revealed that these aberrations are most likely associated with expression of mutant PS1 presenilins residing in the endoplasmic reticulum [269]. In the Tg5469 AD mouse which over-expressed APP, the SOCE was not changed, whereas deletion of APP caused an inhibition of store-operated Ca^{2+} entry [164]. This inhibition may be associated with down-regulation of expression of either TRPC1 or Orai 1 channels.

11.6.5 Pathological Ca^{2+} Signalling in Astrocytes In Vivo

Imaging astroglial $[Ca^{2+}]_i$ dynamics in vivo in the brains of AD animal models reliably demonstrated aberrant, hyperactive $[Ca^{2+}]_i$ dynamics, which is fundamentally similar to neuronal hyperexcitability routinely observed in AD-like experimental pathology [350]. Aberrant hyperactive $[Ca^{2+}]_i$ oscillations have been observed in reactive astrocytes associated with senile plaques. High levels of resting $[Ca^{2+}]_i$, pathological Ca^{2+} oscillations and long-projecting propagating Ca^{2+} waves have been identified in plaque-associated astrocytes in the brains of APP/PS1 mice [138]. Emergence of astroglial Ca^{2+} hyperactivity was also suggested to be linked with abnormal purinergic signalling in reactive astrocytes. There are claims that reactive astrocytes release excessive amounts of ATP through connexin hemichannels. This ATP, acting in autocrine manner, activates astroglial P2Y purinoceptors, which mediate pathological Ca^{2+} signalling [62]. An increased frequency of astroglial Ca^{2+} oscillations was also observed in AD animals in the pre-plaque stage, and these abnormal $[Ca^{2+}]_i$ dynamics coincided with the instability of vascular tone probably indicating that astrocytes in their ability to regulate local blood flow [278].

11.6.6 Astroglial Ca^{2+} Signalling Toolkit Is Remodelled in AD

The AD as a chronic pathology leads to a substantial remodelling of astroglial Ca^{2+} signalling toolkit. Chronic exposure of cultured astrocytes to β-amyloid as well in vivo AD pathology (in model animals) changes expression of various components of Ca^{2+} homeostatic/signalling system; these molecules include, for example, metabotropic and ionotropic receptors, intracellular Ca^{2+} channels, store-operated Ca^{2+} channels and Ca^{2+} sensors [162, 163, 309].

Exposure of astroglial cultures to 10–30 μM β-amyloid$_{1–40}$ for 48–72 h resulted in an increase of the amplitude of $[Ca^{2+}]_i$ transients in response to stimulation of metabotropic glutamate receptor mGluR5. This augmentation of metabotropic Ca^{2+} signalling was a consequence of an up-regulated expression of mGluR5 detected at both mRNA and protein levels [47]. This was corroborated in another series of experiments which demonstrated that 24–72 h exposure of cultured astrocytes to 100 nM–20 μM of oligomeric β-amyloid increased expression of mGluR5 [93, 94, 161]. This up-regulation of mGluR5 expression was suppressed by the inhibitors of calcineurin and Nf-κB (nuclear factor κ-light-chain-enhancer of activated B cells) [161]. Similar increase in expression of mGluR5 was detected in astrocytes in the animal AD models and in post-mortem human tissues. Increased levels of mGluR5 protein were found in the post-mortem hippocampal preparations obtained from AD patients at advanced (Braak V–VI) stages of the disease [47, 161]. Incubation of astrocytes with nanomolar (0.1–100 nM) concentrations of β-amyloid$_{1–42}$ for 24–72 h increased the expression of several subunits of nicotinic cholinoreceptors including α7nAChR, α 4nAChR and β2nAChR [335]. Similarly, increased levels of α7nAChR were identified in the post-mortem brain tissue of patients with sporadic AD and familial AD associated with the Swedish APP mutation [341].

Another important class of molecules affected by AD progression is represented by intracellular Ca^{2+} release channels. Exposure of cultured astrocytes to 125 nM of Tat-ProADAM10709–729 peptide (this peptide inhibits production of β-amyloid$_{1–40}$ and β-

amyloid$_{1–42}$) for 72 h leads to an increased expression of InsP_3R1 [93]. Sim ilarly, up-regulation of expression of InsP_3R1 and InsP_3R2 mRNA was detected in astrocytes in vitro which were exposed to 100 nM oligomeric β-amyloid$_{1–42}$ [161]. Pathological remodelling of Ca^{2+} homeostatic and signalling cascades differ between different brain regions. Expression of InsP3R1 is increased in healthy hippocampal astrocytes exposed to β-amyloid, but remains unchanged in astrocytes from the entorhinal cortex [94]. However, β-amyloid did not affect expression of InsP_3R1 in astrocytes isolated from 3xTg-AD animals, indicating that exogenous β-amyloid and over-expression of mutated AD-related genes share common molecular pathways that cause deregulation of Ca^{2+} homeostasis. In post-mortem studies, however, generalised decrease in the expression of InsP_3Rs was detected in all brain regions including frontal, parietal and entorhinal cortices and the hippocampus [102, 141, 340]. These studies did not, however, discriminate between cell types. Many other components of Ca^{2+} signalling system are affected by AD; these include components calpain-10 [85], NFAT (Nuclear factor of activated T-cells) [1], NF-κB [93], calcineurin [93, 199], L-type calcium channels [59] and store-operated Ca^{2+} channels [239]. All in all 32 genes associated with Ca^{2+} signalling were found to be affected in the transcriptome of astrocytes microdissected from patients with different Braak stages of AD. It appeared that expression of several isoforms of calmodulin kinase CaMKII, two isoforms of calmodulin, plasma membrane Ca^{2+}-ATPases, ryanodine receptors and InsP3Rs, was decreased at advanced (Braak V–VI) stage when compared with early (Braak I–II) stage of the disease [262].

11.6.7 Ca^{2+} Release and Astroglial Reactivity

As has been alluded before, astrogliosis is a prominent component in certain brain regions in the context of AD; reactive astrocytes associate themselves with senile plaques in human tissue and in the brains of AD animal models, arguably forming a defensive barrier protecting neural networks [106, 306]. Suppression of astrogliotic response (for instance, by genetic deletion of GFAP and vimentin) exacerbates β-amyloid load and facilitates plaques dissemination [137]. Astroglial reactivity, however, is different in different regions of the brain. Prominent astroglial reactivity is observed in the hippocampus, whereas the emergence of senile plaques and β-amyloid depositions does not trigger astrogliosis in entorhinal and prefrontal cortices of AD mice models. Underlying molecular mechanisms might be linked to a deficient Ca^{2+} signalling in astrocytes from different brain regions.

In the AD context, one of the most relevant signals instigating astroglial reactivity is β-amyloid, and indeed exposure of astroglia to β-amyloid in vitro or in situ triggers astrogliosis [4, 306]. As has been described above, β-amyloid also evokes $[Ca^{2+}]_i$ elevation. It appears that β-amyloid-induced Ca^{2+} signals originate from Ca^{2+} release from the endoplasmic reticulum Ca^{2+} store and these Ca^{2+} signals are directly linked to the initiation of astrogliotic response. Suppression of Ca^{2+} release from the ER with pharmacological tools effectively inhibits astrogliosis induced by β-amyloid in both cultured astrocytes and astroglia in organotypic slices [4]. The causal role of Ca^{2+} release in astroglial reactivity was directly demonstrated: deletion of InsP_3R2 effectively suppressed astrogliotic activation [120]. Sensitivity of astrocytes from different brain regions to β-amyloid is different: β-amyloid up-regulates expression of molecules providing for ER Ca^{2+} release in hippocampal

but not in entorhinal astrocytes [94]. This may explain the absence of astrogliotic defensive response in astrocytes from cortical regions, which renders these parts of the brain vulnerable to the AD pathology [162, 300].

11.7 AD Pathology Affects Astroglial Vesicular Trafficking and Secretion

Astrocytes are secretory cells, being a part of CNS-wide “gliocrine” system [301]. Astrocytes are known to secrete ~200 molecules, many of which are released through exocytosis of secretory vesicles [349]. Intracellular astroglial vesicles are also fundamental for delivery of various molecules [298] such as ion channels, membrane receptors and transporters, as well as major histocompatibility complex II (MHC-II, [296]) and EAAT 2 [266], to the plasma membrane. Vesicular traffic is controlled by sophisticated molecular cascades, which in turn are regulated by increases in $[Ca^{2+}]_i$ [220, 266]. Changes in $[Ca^{2+}]_i$ differentially regulate motility of distinct vesicles types. Increases in $[Ca^{2+}]_i$ reduce the motility of vesicles carrying peptides, such as atrial natriuretic peptide, while accelerating motility of vesicles containing vesicular L-glutamate transporter VGLUT1 [218–220]. Proteolytic enzymes stored in endolysosomes may contribute to the development of AD. One of these proteases is represented by the insulin-degrading enzyme (IDE), which, when secreted into the extracellular space, may degrade β-amyloid. Astrocytes are the main cell type which produces and releases IDE [68, 263]. It has been hypothesised that in AD the capacity of secreting IDE is reduced, leading to an increase in β-amyloid, which involves a reduction in autophagy-based lysosomal secretion of IDE [263].

Astrocytes from 3xTg-AD mice demonstrated an aberrant vesicular traffic. Spontaneous mobility of peptidergic and endolysosomal vesicles as well as the ATP-evoked, Ca^{2+}-dependent, vesicle mobility was all diminished in AD astrocytes (Fig. 11.9). Transfection of healthy rat astrocytes to express familial AD-associated mutated presenilin 1 (PS1M146V) caused very similar impairment of peptidergic vesicle trafficking. The stimulation-dependent peptide secretion from single vesicles was less efficient in 3xTg-AD and PS1M146V-expressing astrocytes than in healthy controls. The impaired vesicle dynamics and reduced evoked secretion of the signalling peptides both may contribute to the development of AD [269].

11.8 GABAergic Astrocytes in AD

In the healthy young CNS, astrocytes contribute to GABAergic transmission through (i) supplying glutamine, needed for GABA biosynthesis in neuronal terminals and (ii) removing ~20% of all released GABA by dedicated plasmalemmal transporters GAT-1 and GAT-3. After being transported into the astrocytes, most of GABA is catabolised by GABA transaminase (GABA-T) to succinate, which is subsequently utilised for production of ATP [253, 305, 319]. Due to this energy-oriented catabolism, the concentration of GABA in the cytosol of astrocytes is rather low. Ageing and neurodegeneration, however, significantly affect astroglial GABA metabolism; concentration of GABA in astrocytes in elderly [155], in patients with AD [118, 332] and in transgenic AD models [41, 118, 332], is significantly higher. This increase is particularly prominent in reactive astrocytes associated with senile plaques in AD animal models; intracellular GABA concentration in these AD reactive

astrocytes is several times higher than in age-matched controls and is very similar to neuronal GABA content [41, 118, 332]. These changes in astrocytic GABA content in reactive astrocytes are accompanied with an up-regulation of expression of GABA producing enzyme glutamic acid decarboxylase GAD67 as well as with an increase in expression of astroglia-specific monoaminoxidase-B (MAO-B) [118]. At the same time, expression of glutamine synthetase is specifically down-regulated in reactive astrocytes surrounding senile plaques in the hippocampus and prefrontal cortex of 3xTg-AD mice (Fig. 11.10 and [204]). Thus reactive astrocytes acquire machinery to synthetase GABA either from glutamate (through GAD67 and increased glutamate availability due to the loss of glutamine synthetase) or from putrescine through MAO-B pathway [84]. Furthermore, there is an increased glutamatergic neuronal activity around senile plaques [206]; this conceivably increases astroglial glutamate uptake and availability of cytosolic glutamate for conversion to GABA cytosolic glutamate concentration glutamate transport into astrocytes Astroglial GABA may potentially be released from astrocytes by diffusion through Bestrophin-1 Cl^- channels or through reversed GAT3 transporters (Fig. 11.11, [84]). The emergence of GABAergic astrocytes may represent yet another defensive response; as GABA release from astroglia may counteract neuronal hyperexcitability by an increase of tonic inhibition [84].

11.9 Astrocytes as Therapeutic Targets in AD

Neuroglia is yet to be considered as a fundamental target for novel therapeutic agents for neurological disorders and neurodegenerative diseases in particular. It is conceivable that by modulating the status of astrocytes, by reversing or halting astrocytes degeneration and asthenia or by modulating astroglial reactivity, the course of AD can be altered and the disease can be delayed or cognitive alterations reversed. Several possible strategies that may affect astroglial pathology have recently emerged.

11.9.1 Lifestyle Changes May Reverse Astrodegeneration

Recent experiments have demonstrated that environmental modifications such as sensory stimulation, dieting or usage of food supplements may affect AD progression and at the same time change astroglia morphology and revert astroglial atrophy. Experiments on APP and 3xTg-AD mice models revealed that chronic exposure of these animals to physical activity and/or to enriched environment reversed morphological atrophy of astrocytes, increased GFAP expression and normalised GFAP-positive astroglial profiles (Fig. 11.12); most importantly, these astroglia-specific changes developed in parallel to a decrease in β-amyloid load [20, 236]. Incidentally, environmental stimulation also improved neurogenesis which is impaired in the AD [231, 233]. Another AD model, the 5xFAD mice chronically treated with polyunsatu-rated fatty acid 2-hydroxy-docosahexaenoic acid similarly rescued astroglial atrophy, restored adult neurogenesis and improved cognitive performance [76]. Treatment with specific diets may also affect ageing and AD progression. It is well appreciated that caloric restriction exerts prominent positive effect of lifespan of several species and may boost cognitive resilience of the brain [80, 169, 170, 175]. It appeared that caloric restriction induces growth of astroglial perisynaptic processes, thus extending synaptic coverage, preventing glutamate spillover, improving K^+ buffering and glu tamate uptake from the synaptic cleft, thus ultimately enhancing synaptic plasticity [217].

11.9.2 Preventing Neurodegeneration by Adrenergic Astroglial Excitation

Noradrenergic innervation of the CNS is provided by projections of adrenergic neurones localised in the brainstem nucleus locus coeruleus. This small nucleus is located near the fourth ventricle and, in humans, comprises around 50,000 neurones [188]. Diffuse innervation by projections of locus coeruleus neurones reaches practically all parts of the brain and the spinal cord [25]. The locus coeruleus neurones are vulnerable to oxidative stress; apparently, they are lost in ageing and they are first to die during neurodegeneration including AD [75, 167, 190, 249]. Astrocytes, being universally sensitive to noradrenaline, represent the major target for deficient noradrenergic innervation and interfering with astroglial adrenergic mechanisms may be therapeutically relevant [348].

Astroglial sensitivity to noradrenaline, released from locus coeruleus neuronal projections, is mediated by both α- and β-adrenoceptors linked, respectively, to cytosolic Ca^{2+} signalling [66, 131] and cyclic AMP (cAMP) cascades [297]. In the in vivo experiments in the awake mice, the vast majority of astrocytes generated synchronous $[Ca^{2+}]_i$ signals in response to noradrenaline released from locus coeruleus projections [22, 66, 210]; of note neurones did not generate Ca^{2+} responses to the same stimulation [208]. This difference reflects upon much higher density of adrenoceptors in astrocytes when compared to neurones [10]. Degeneration of locus coeruleus neurones associated with ageing most certainly impairs adrenoceptors–medicated astroglial excitability, which may be linked to the cognitive decline [348]. Consequently, preventing death of locus coeruleus neurones or boosting astroglial adrenergic excitability may represent a valid therapeutic strategy [348]. Alternative possibilities may involve drugs, such as deprenyl, that limit noradrenaline catabolism in astrocytes.

Transcranial direct current stimulation (tDCS) was used with positive effects including memory enhancements, accelerated motor function rehabilitation, alleviation of depressive symptoms and decelerated progression of cognitive impairments in AD patients [140, 197]. The mechanism of action of tDCS is astroglial and noradrenergic. It has been revealed that tDCS induces a massive increase in astroglial $[Ca^{2+}]_i$ which has been suppressed by the ablation of noradrenergic neurones or by the inhibition of α_1-adrenoceptors [186]. Alternative possibilities may involve drugs that limit noradrenaline catabolism in astrocytes such as, for example, deprenil.

11.10 Conclusions

Astroglial contributions to the pathophysiology of AD are complex and range from early astroglial atrophy, which limits homeostatic support and may cause synaptic weakness and early cognitive decline, to astroglial reactivity, which seems to protect the CNS against AD-associated pathology and limits the spread of β-amyloid load. Astroglia may also undergo pathological remodelling, in which astrocytes may acquire new functions such as, for example, secreting GABA. Specific manipulations with astroglia may represent a valid therapeutic approach for treating neurodegenerative disorders including AD.

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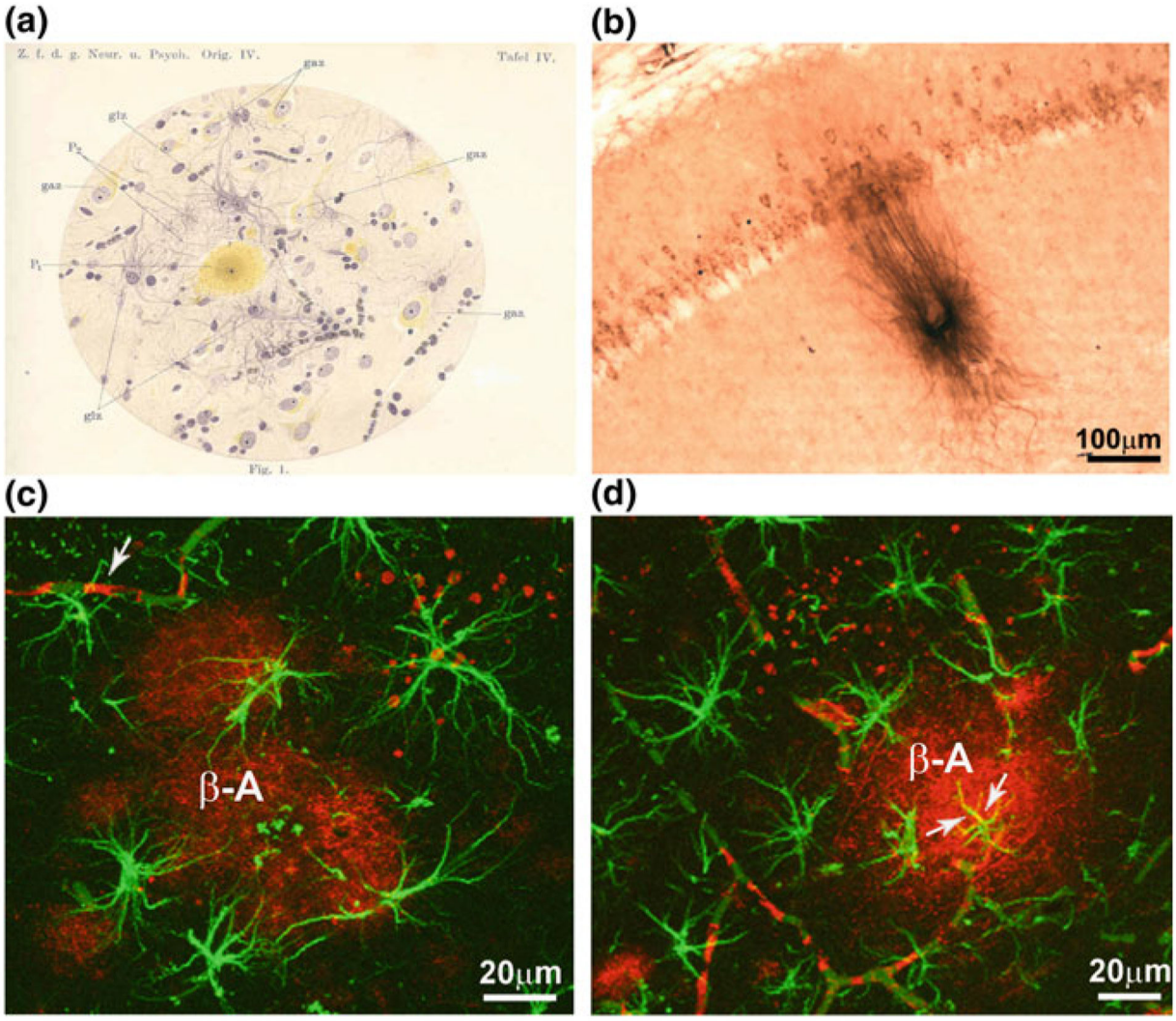

Fig. 11.1.

Glial cells in AD **a** Alois Alzheimeŕs drawing illustrating the glial reaction (astro- and/or micro-gliosis and hypertrophy) in a pathological brain containing senile plaques. Abbreviations: *gaz*, ganglionic cell—i.e. neurone; *glz*, glial cell, P, central part of the plaque; P_2, peripheral part of the plaque. From [8]. **b** Photomicrograph showing the presence of β-amyloid within the pyramidal neurones of the hippocampal CA1 area as well as the presence of a plaque in 12 months 3xTg-AD mice. **c**, **d** Confocal images showing GFAP-positive (green) reactive astrocytes surrounding β-amyloid plaques (β-A red; **c**). **d** Reactive astrocytes (green) and an astrocyte showing cytoplasmic β-amyloid accumulation (indicated by arrows; co-localisation is in yellow) near a neuritic plaque (red). Modified and adapted with permission from [235]

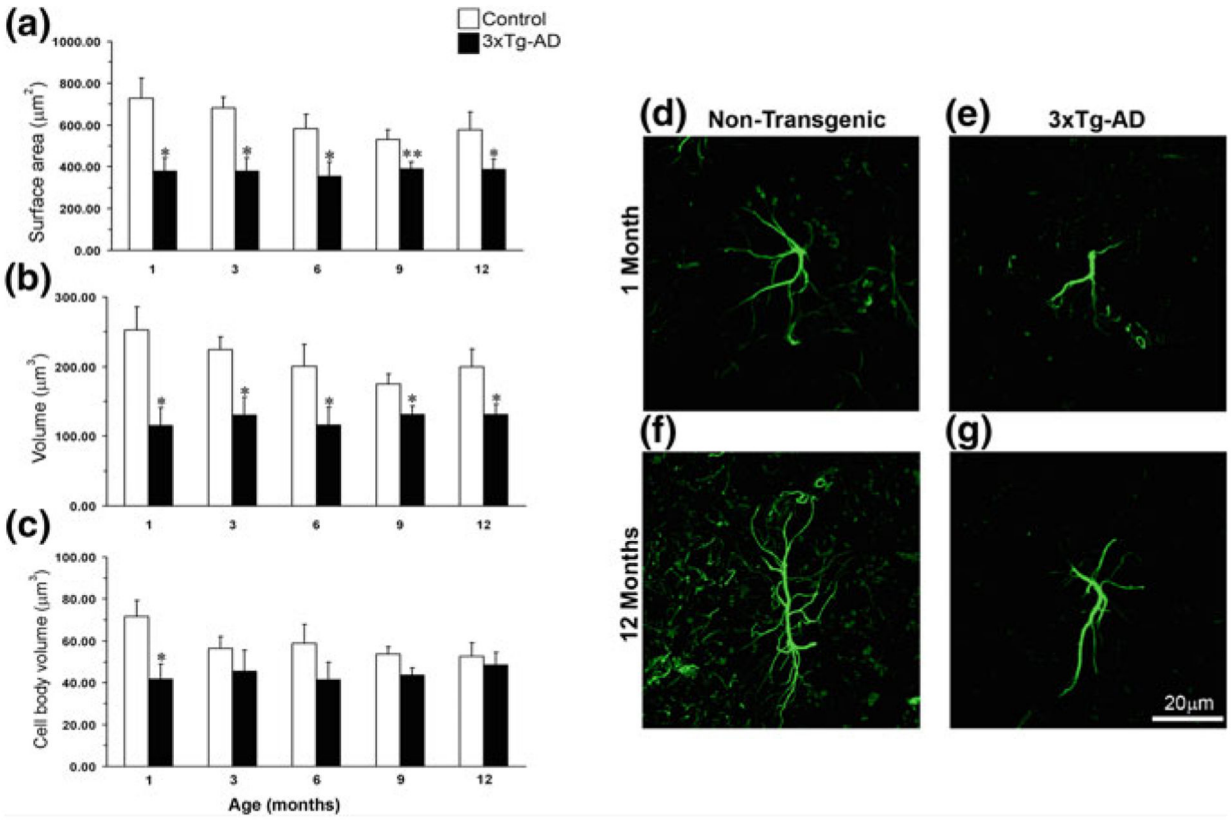

Fig. 11.2.

Astroglial atrophy in the entorhinal cortex (EC) of 3xTg-AD mice. Comparison of astrocytic GFAP surface area and volume in the EC of non-Tg and 3xTg-AD animals of different ages. The histograms show a comparison of **a** surface area, **b** total cell volume and **c** somata volume in the EC at the ages of 1, 3, 6, 9 and 12 months between 3xTg-AD and non-Tg animals. Results are means ± S.E.M. (*$p < 0.05$ compared with the age-matched non-Tg control). Confocal micrographs show astrocytic atrophy in 3xTg-AD at 1 month (**e**) and 12 months (**g**) compared with the control animals (**d**, **f**). Reproduced with permission from [338]

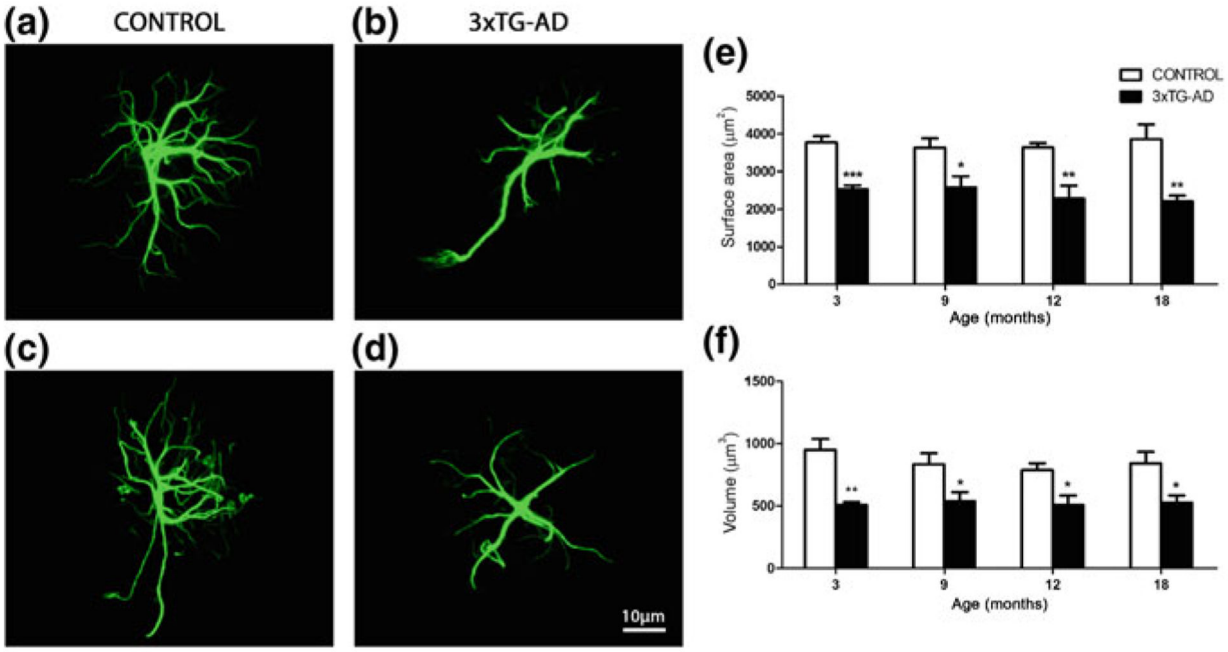

Fig. 11.3.

Astroglial atrophy in the prefrontal cortex of 3xTg-AD mice. Confocal images showing morphology of GFAP-positive astrocytes in control non-Tg animals and astrocytic atrophy in the 3xTg-AD animals at 3 months (**a** and **b**, respectively) and 18 months (**c** and **d**, respectively) in the prefrontal cortex. Bar graphs showing the decreases in the surface area and volume (**e**, **f**) in 3xTg-AD mice when compared with control animals. Bars represent mean ±SEM. Reproduced with permission from [139]

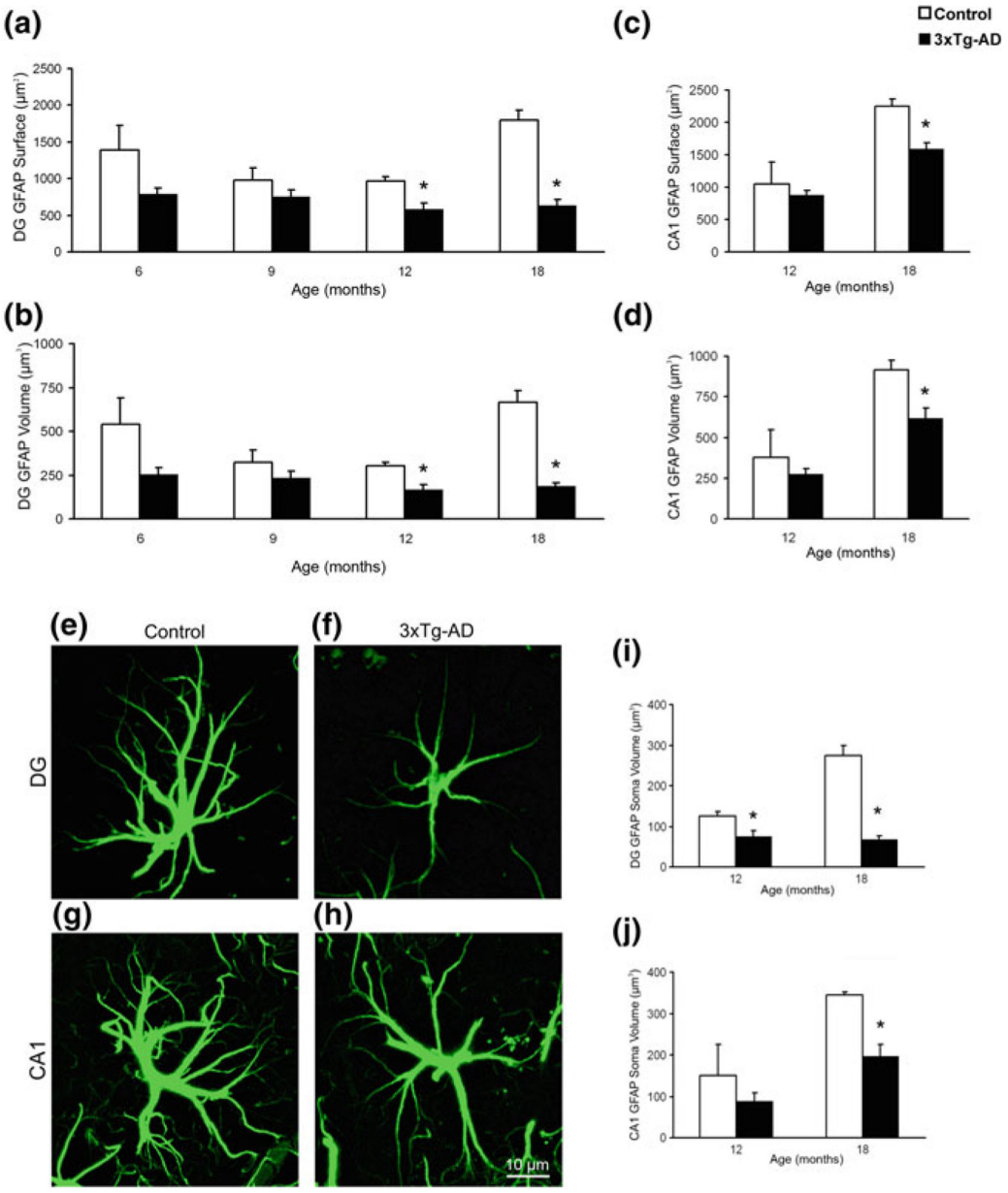

Fig. 11.4.

Astroglial atrophy in the hippocampal areas of 3xTg-AD mice. Bar graphs showing the significant decrease in surface area, volume, and soma volume of GFAP-positive astrocytes in the dentate gyrus (DG) (**a**, **b**, **i**) and the CA1 region (**c**, **d**, **j**) of the hippocampus of the 3xTg-AD mice when compared with control animals. Bars represent mean ± SEM ($p < 0.05$). (**g**–**j**). Confocal micrographs illustrating the astrocytic atrophy in 3xTg-AD mice in the DG (**f**) and CA1 (**h**) compared to control animals (**e** and **g**). Reproduced with permission from [203]

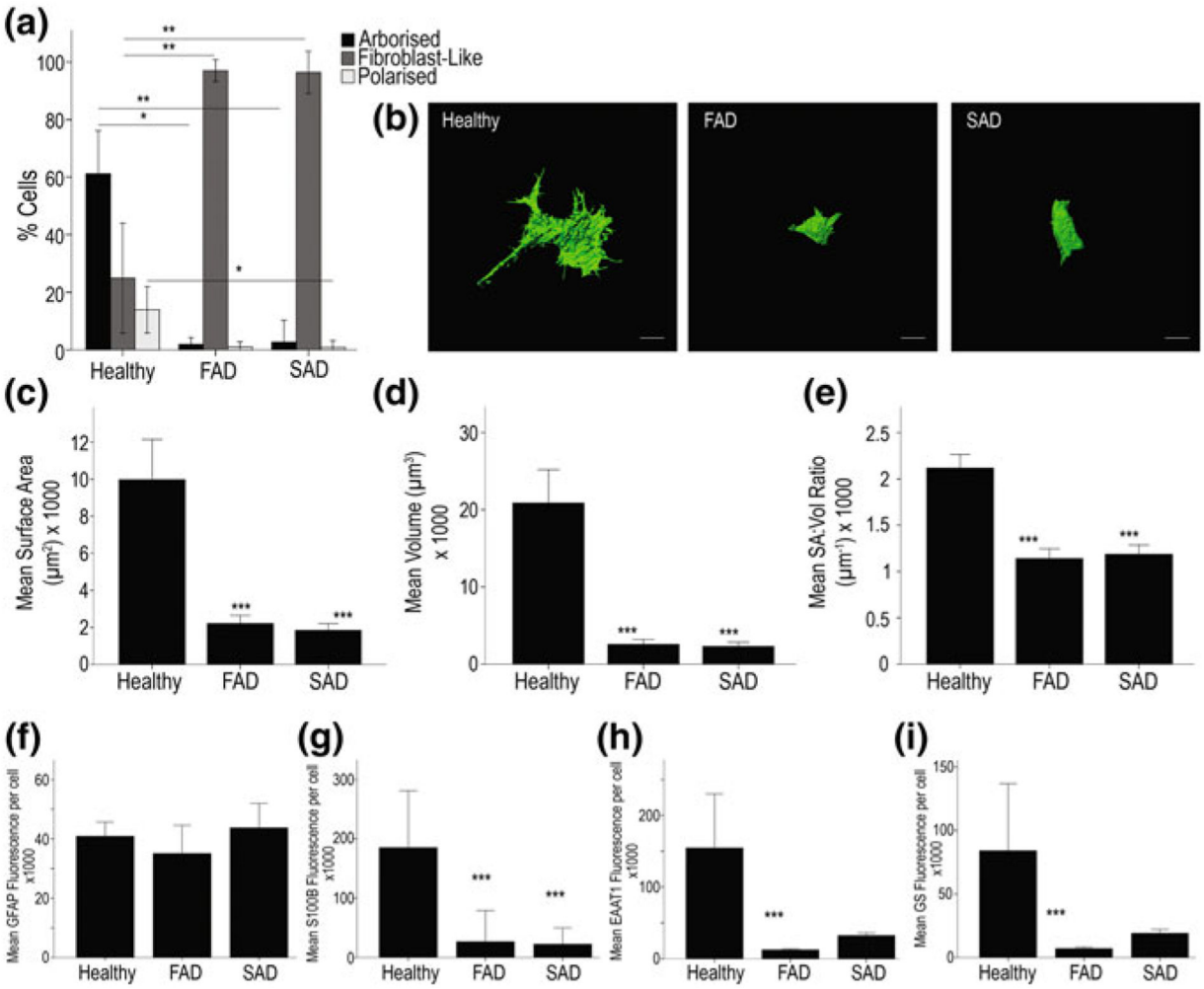

Fig. 11.5.

Astrocytes derived from *PSEN1* M146L FAD and *ApoE4*$^{+/+}$ SAD patients exhibit significant atrophy when compared to those from healthy patients. **a** Exemplar 3D isosurface renders constructed from serial confocal z-stacks display clear differences in cell size and overall morphology (**b**). Scale bar = 10 μm. Quantification of cells using these renders by way of surface area (**c**), cell volume (**d**) and SA:Vol ratio (**e**) reveal significant differences in all aspects of cellular morphology between healthy and diseased astrocytes. Quantification of mean fluorescence intensity per immunoreactive cell reveals no significant difference in GFAP staining intensities between AD and control astrocytes (**f**) but S100B, EAAT1 and GS intensities are reduced in both FAD and SAD cells (**g**, **h** and **i**, respectively). Asterisks on graph; ***$p < 0.001$, **$p < 0.005$, *$p < 0.05$. Reproduced from [119]

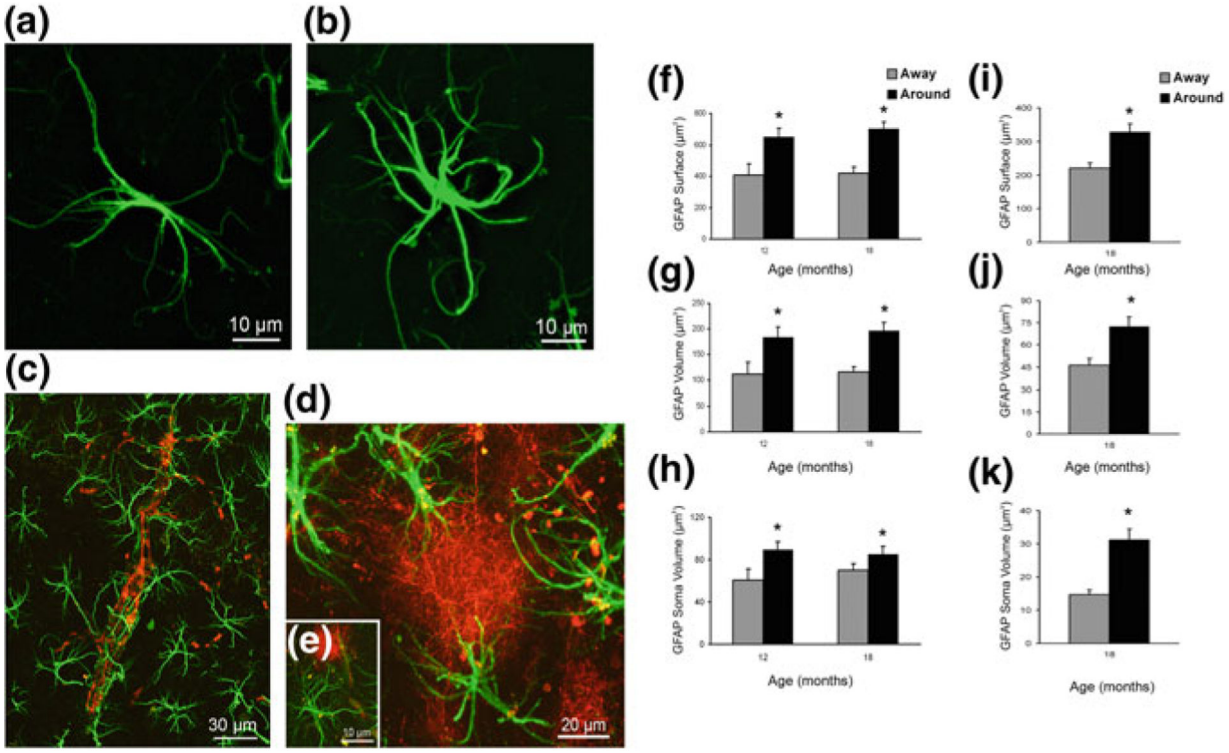

Fig. 11.6.

Concomitant astroglial atrophy and astrogliosis at the advanced stages of AD-like pathology in 3xTg-Ad mice. **a**, **b** Confocal images of hippocampal preparations dually labelled by GFAP and by anti-β amyloid monoclonal antibody illustrating differential changes in GFAP profiles in astrocytes distant to the plaques (**a**) and associated with the β-amyloid plaques (**b**). **c**–**e** Confocal dual labelling images (GFAP in green and β-amyloid in red) in 3xTg-AD mice showing the accumulation of astrocytes around the β-amyloid plaques and vascular β-amyloid deposits. Astrocytes surrounding β-amyloid plaques (**d**, **e**) and β-amyloid deposits around a blood vessel (**c**), undergo astrogliosis. **f**–**k** Bar graphs showing GFAP-positive astrocytic surface area (**f**), volume (**g**) and somata volume (**h**) differences between astrocytes located around the β-amyloid plaques (Aβ) and those distant to the plaques in the CA1 of 3xTg-AD animals. **i**–**k** Similar astrocytic surface area (**i**), volume (**j**) and somata volume (**k**) differences are observed in the DG at 18 months of age. Bars represent mean 6 SEM ($p < 0.05$). Reproduced with permission from [203]

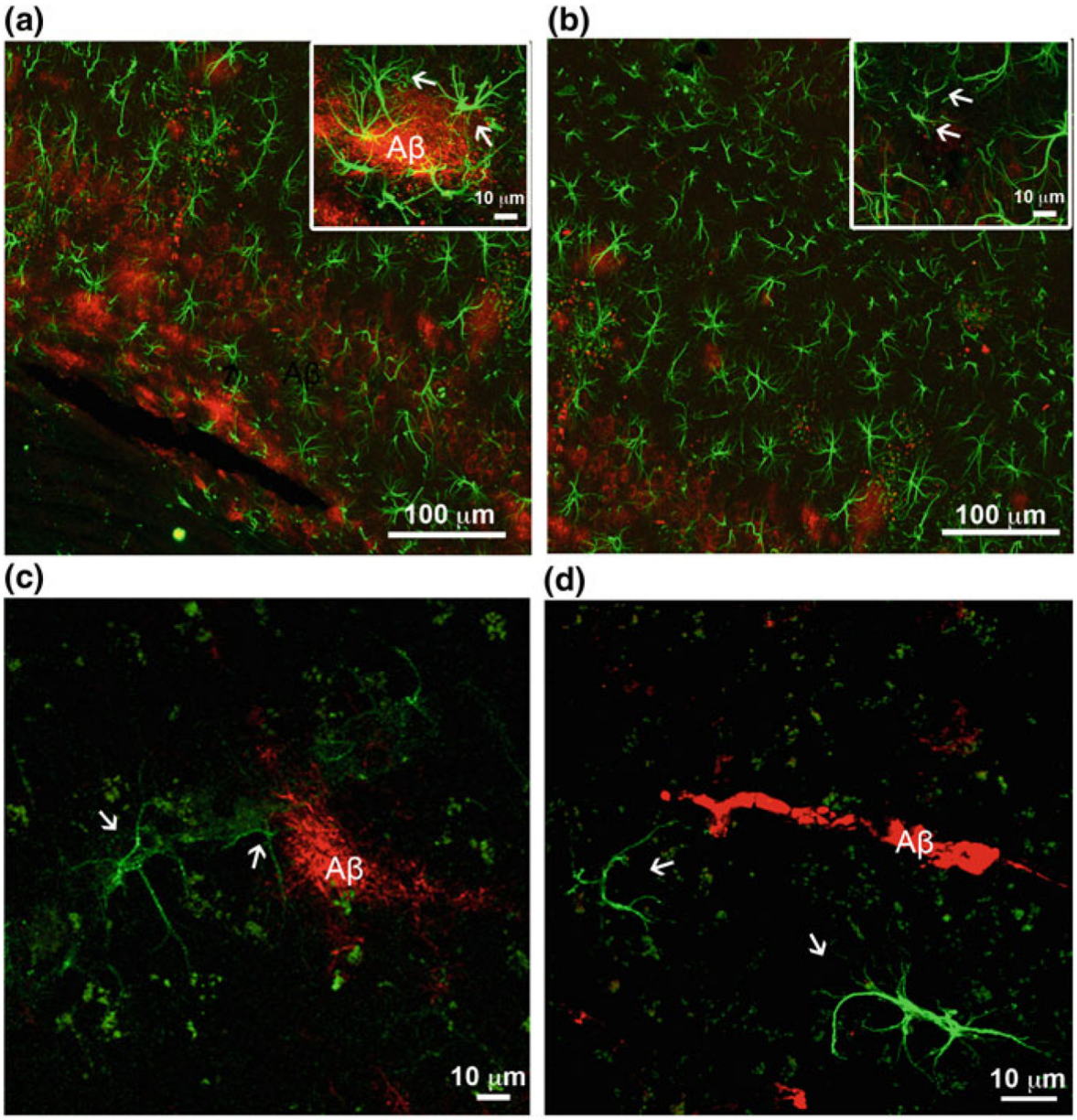

Fig. 11.7.

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 labelled by 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 (arrows) distant from β-amyloid deposits (**b**) in 3xTg-AD mice. **c**, **d** Confocal dual labelling images (GFAP in green and β-amyloid in red) showing the 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**). Modified and reproduced with permission from [300, 338]

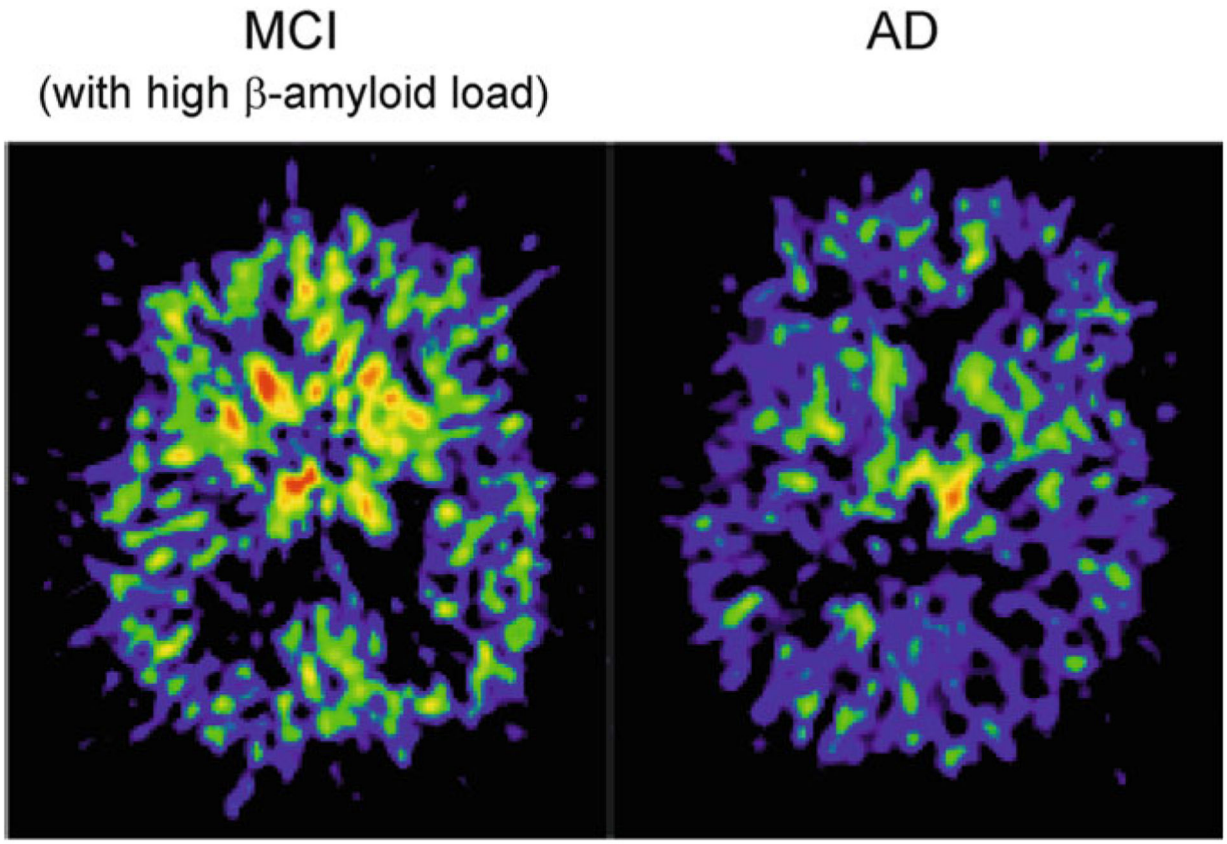

Fig. 11.8.

Failure in astroglial reactivity defines the switch between mild cognitive impairment and senility in AD. Prominent astrogliosis in the brain of patient with mild cognitive impairment associated with high β-amyloid load (*Left panel*) in comparison with patient with Alzheimer's disease (*Right panel*). Representative images of ^{11}C-d-deprenyl binding (that reflects MAO-B expression in astrocytes) were obtained by position emission tomography. The MCI patient 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 PET scans show sagittal sections of the brain at the level of basal ganglia. Colour scale indicates red = very high, yellow = moderately high, green = high, blue = low ^{11}C-d-deprenyl binding. Photo courtesy of A. Nordberg, Karolinska institutet. Reproduced with permission from [300]

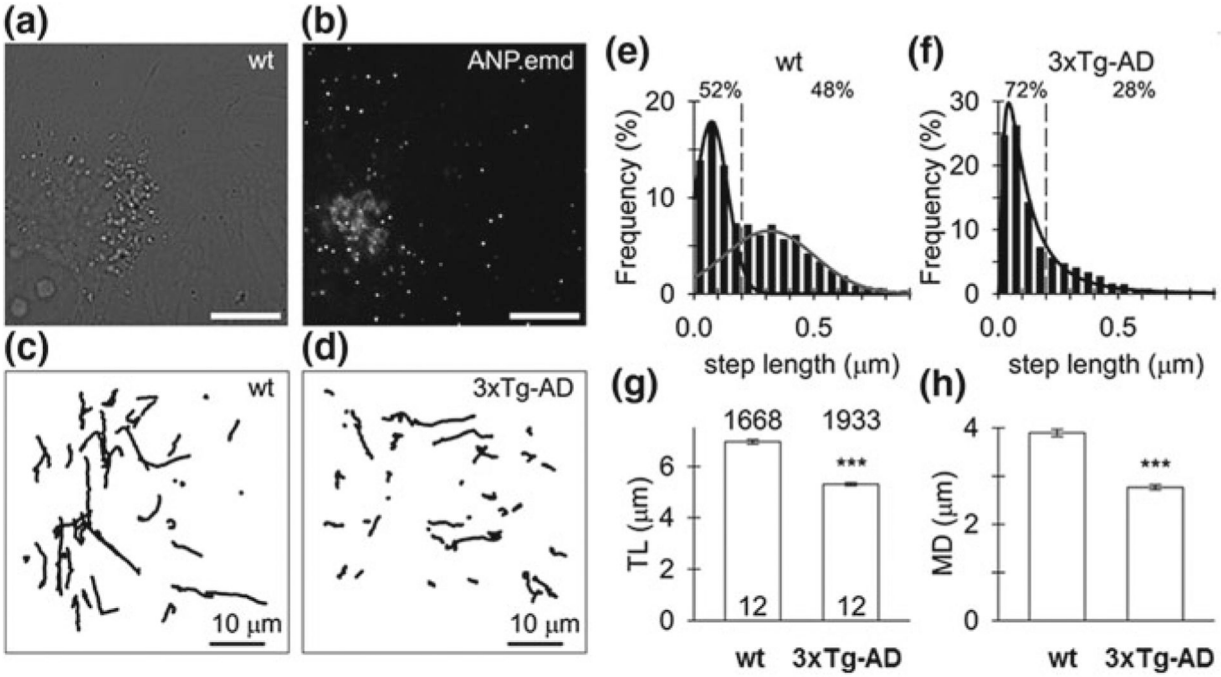

Fig. 11.9.

Decreased spontaneous mobility of peptidergic vesicles in 3xTg-AD astrocytes. **a** Live cultured wild-type (wt) astrocyte under DIC optics and **b** the confocal image of the same cell expressing fluorescent peptide atrial natriuretic peptide-emerald green (ANP.emd), stored in individual vesicles, observed as bright fluorescent puncta; scale bars, 10 μm. **c** Vesicle tracks ($N = 50$) obtained in a 15-s epoch of imaging representative control (wt) and **d** 3xTg-AD astrocytes expressing ANP.emd, respectively. Note less elongated vesicle tracks in the 3xTg-AD astrocyte. **e**, **f** Frequency histogram of the step length in spontaneously moving vesicles in wt ($N = 5025$, **e**) and 3xTg-AD ($N = 5072$, **f**) astrocytes. The data were fitted with the function $f = a \times \exp(-0.5 \times (x/x_0)/b)^2/x$, where $a = 17.88 \pm 0.00\ \mu m^{-0.5}$, $x_0 = 0.07 \pm 0.00$ μm(black curve) and $a = 6.53 \pm 0.13$, $b = 0.19 \pm 0.01\ \mu m^{-0.5}$, $x_0 = 0.31 \pm 0.01$ μm (grey curve) in wt astrocyte, and with the function $f = a \times \exp(-0.5 \times (\ln x/x_0)/b)^2/x$, where $a = 1.96 \pm 0.04$, $b = 0.92 \pm 0.02\ \mu m^{-0.5}$, $x_0 = 0.10 \pm 0.00$ μm (black curve) in 3xTg-AD astrocyte. The indicates the step length of 0.2 μm obtained close to the intersection of distributions (black and grey curve) in wt astrocytes to discriminate small (<0.2 μm) from large (≥ 0.2 μm) steps. Note the higher proportion (%) of smaller steps lengths in the 3xTg-AD astrocyte indicated by the absence of the second mode distribution seen in wt astrocytes. **g** Track length (TL), **h** maximal displacement (MD),note substantially diminished TL, MD in 3xTg-AD astrocytes. The numbers above the top of the bars (mean ± SEM) indicate the number of vesicles analysed; the numbers at the bottom of the bars indicate the number of cells analysed; "***" —indicates p values < 0.001. Modified with permission from [269]

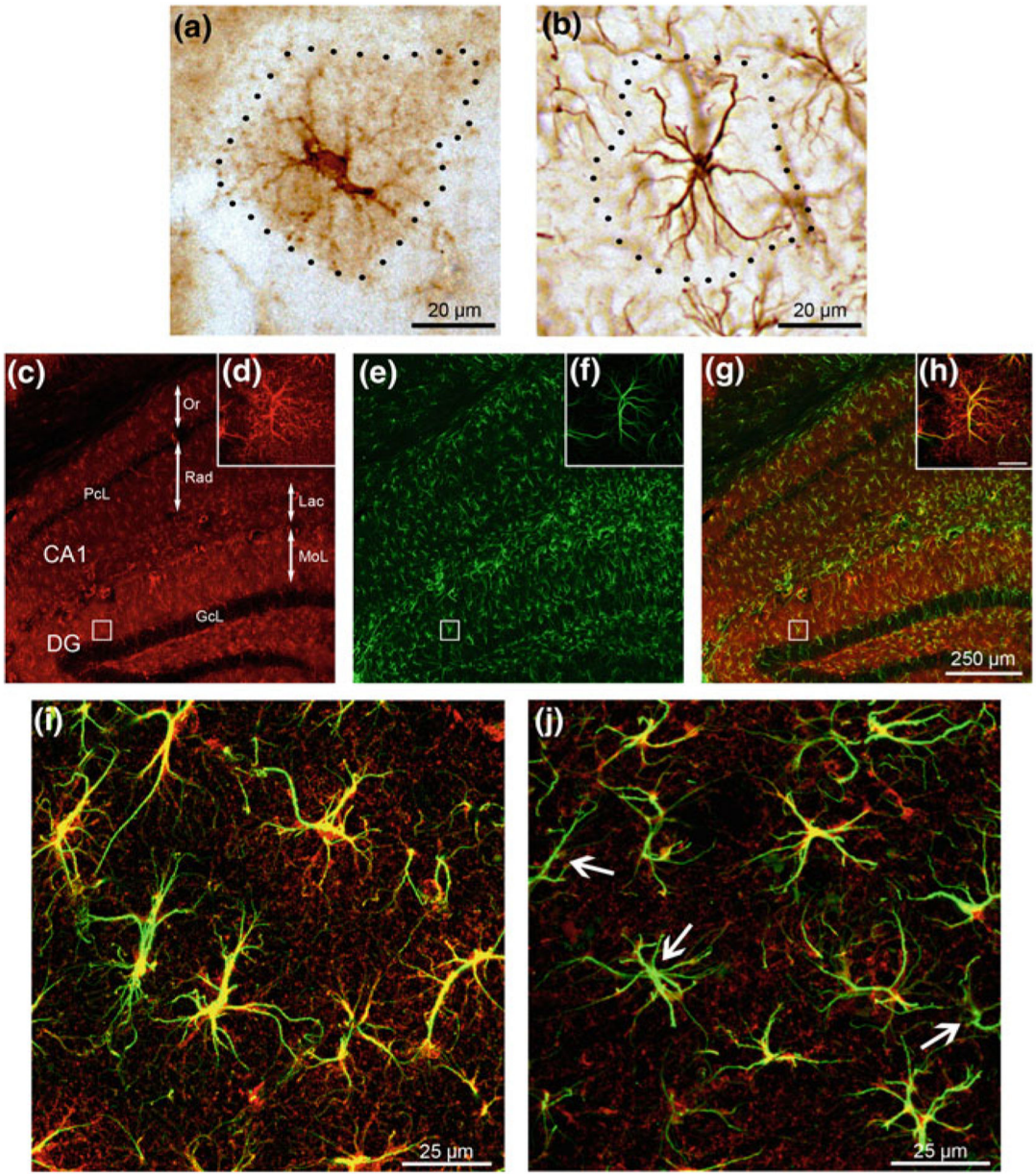

Fig. 11.10.

Down-regulation of glutamine synthetase (GS) expression in hippocampal astrocytes in 3xTg-AD mice. **a**, **b** Light microscopy images of GS—(**a**) and GFAP—(**b**) positive astrocytes. **c**, **e**, **g** Confocal images of hippocampal preparation labelled for GS (**c**, red), GFAP (**e**, green) and their co-localisation (**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; MoL, molecular layer; Lac, stratum lacunosum moleculare; Or, stratum oriens; PcL, pyramidal layer; Rad, stratum radiatum. Modified and reproduced with permission from [204]

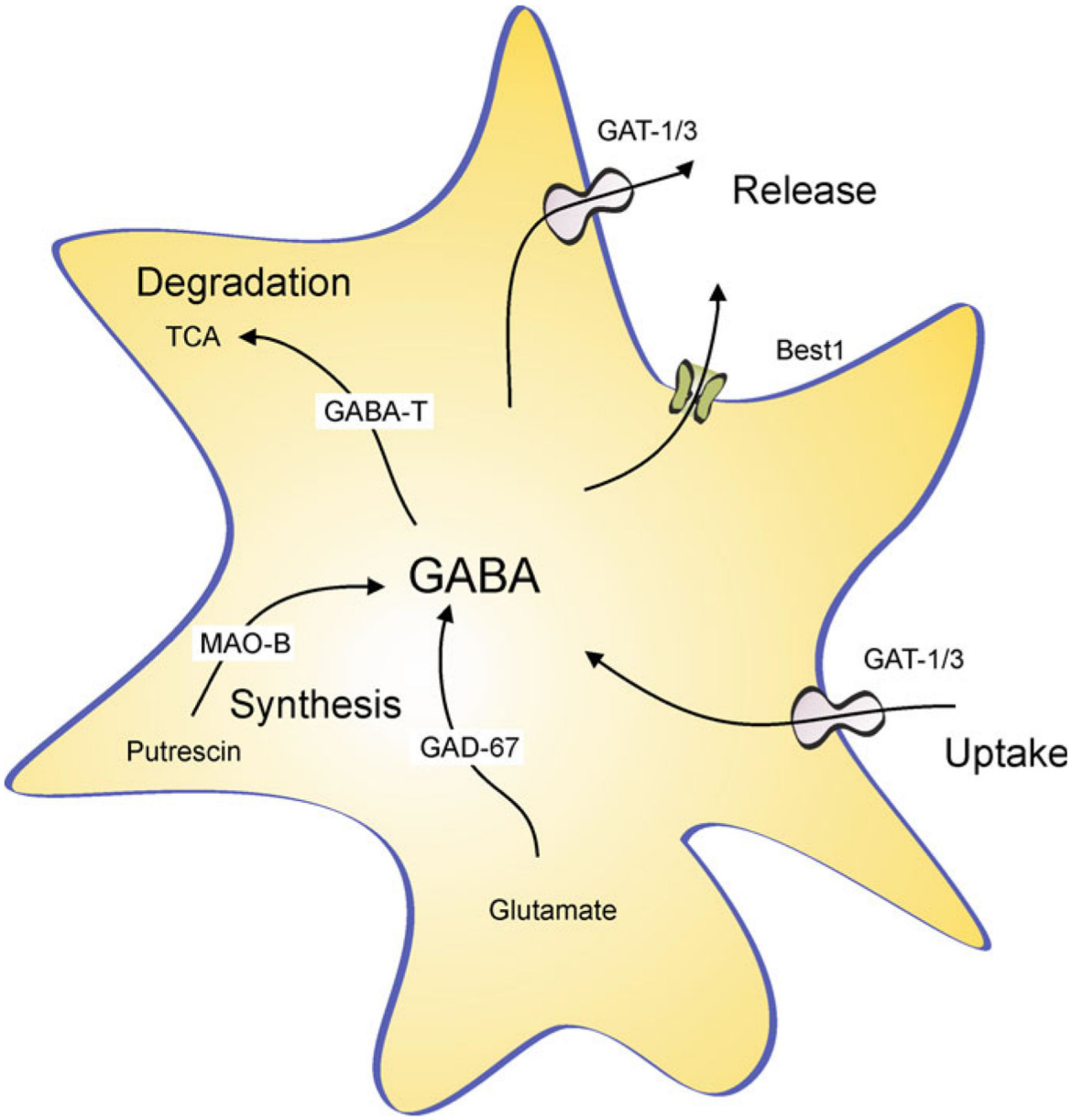

Fig. 11.11.

GABAergic reactive astrocytes in AD. See text for explanation. Abbreviations: GAT1/3 GABA transporters 1 (SLC6A1) and 3 (SLC6A11); Best1—bestrophin 1 anion channel 1; GABAT—GABA transaminase; TCA—tricarboxylic acid (Krebs) cycle; MAO-B—Monoamine oxidase B; GAD67—glutamate decarboxylase. Modified from [84]

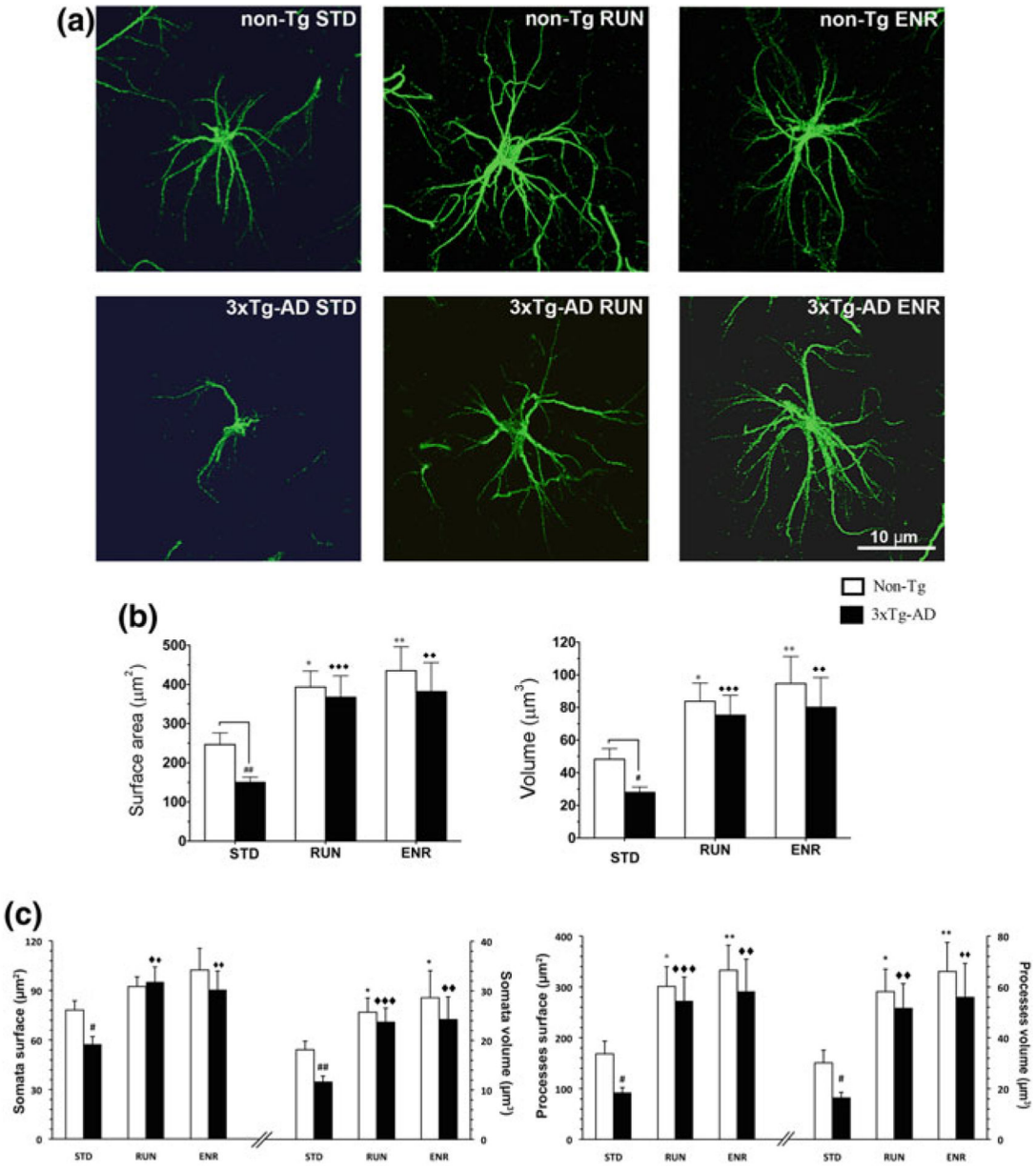

Fig. 11.12.

Environmental stimulation (enriched environment, ENR and physical activity, RUN) reverse morphological atrophy of astrocytes seen in the dentate gyrus isolates from 3xTg-AD mice. GFAP-immunoreactivity of astrocytes in the DG of non-Tg and 3xTg-AD animals housed in different conditions. **a** High magnification of representative confocal micrographs showing the astrocytic morphology in mice housed in standard conditions (STD), RUN and ENR. Scale bars, 10 µm. Note the morphological changes of the astrocytes from both genotypes induced by the different living conditions. **b** Histograms showing difference of surface area and volume of GFAP-positive astrocytes in the DG of non-Tg and 3xTg-AD mice housed under different housing conditions. **c** Histograms showing differences in surface area and volume of GFAP-immunoreactivity of astrocytic cell bodies and processes detected between

non-Tg and 3xTg-AD mice housed under different housing conditions. Bars represent means ± S.E.M., #$p < 0.05$, ##$p < 0.01$ compared with non-Tg animals in same housing environment; *$p < 0.05$, **$p < 0.01$ compared with non-Tg mice housed under STD; ◆◆$p < 0.01$ and ◆◆◆$p < 0.001$ compared with 3xTg-AD mice housed under STD. Reproduced with permission from [236]

Table 11.1

Summary of lesion models of Alzheimer's disease. Modified from [232]

Lesion	Cholinergic	Non-cholinergic	Neuropathology	References
Electrolytic	Yes	Yes	Neuronal death	[156, 293]
Excitotoxins (NMDA, Ibotenic acid, Quisalic acid)	Yes	Yes	Neuronal death	[69, 330]
Quinolinic acid	Yes	Yes	Neuronal death	[37]
Colchicine	Yes	Yes	Neuronal death	[258]
Alkaloids	Yes	Yes	Neuronal death	[65]
AF64A	Yes	No	Neuronal death	[53, 97, 318]
192Ig-G saporin	Yes	No	Neuronal death	[325, 327]
Alcohol	Yes	Yes	Neuronal death	[13]
β-Amyloid	No	No	Cholinergic Dysfunction	[88, 211]

Table 11.2

Transgenic mouse and rat models of Alzheimer's disease

Transgenic mouse and rat models	Neuropathology	References
APP_{751SL}	Plaques	[32]
APP/Ld/2	Plaques	[183]
APP_{Swe}	Plaques	[72]
APP Swedish, 695 K670N M671L	Plaques	[272]
$PS1_{M146L}$	Diffused plaques	[32]
$APP_{751SL}/PS1_{M146L}$	Plaques	[32]
$APP_{SWE}/PS1_{dE9}$	Plaques	[250]
APPSwedish and $PS1_{m146L}$	Plaques	[115]
APP_{695SWE}	Plaques	[110]
APP_{V717F}	Plaques	[67]
K670N/M671L and V717F	Plaques	[115]
APP Swedish, 695 K670N-M671L and Indiana V717F	Plaques	[72]
APPSwedish and V717F	Plaques	[51]
V337 M	Tangles	[280]
4R/2 N	Tangles	[281]
TauP301L (4R,2-,3-)	Tangles	[159]
P301L	Tangles	[89]
Tau_{P301L}	Tangles	[12]
P301S/G272V	Tangles	[252]
P301S	Tangles	[6]
G272V, P301L, R406W	Tangles	[72]
Endogenous tau KO	Tangles	[9]
P301L TET-off	Tangles	[224]
7TauTg	Tangles	[113]
Tg2576 × JNPL3 (APP_{SWE})	Plaques and Tangles	[158]
Tg2576 and VLW	Plaques and Tangles	[228]
3xTg-AD	Plaques and Tangles	[202]
Tg478	None	[79]
Tg1116	None	[79]
Tg478/Tg1116	Plaques	[79]
Tg 478/1116/11587	Plaques	[79]
K670M/N671L	Plaques	[132]