HHS Public Access

Author manuscript

Opera Med Physiol. Author manuscript; available in PMC 2016 June 13.

Published in final edited form as:

Opera Med Physiol. 2016 January ; 1: 13–22.

PATHOBIOLOGY OF NEURODEGENERATION: THE ROLE FOR ASTROGLIA

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Abstract

The common denominator of neurodegenerative diseases, which mainly affect humans, is the progressive death of neural cells resulting in neurological and cognitive deficits. Astroglial cells are the central elements of the homoeostasis, defence and regeneration of the central nervous system, and their malfunction or reactivity contribute to the pathophysiology of neurodegenerative diseases. Pathological remodelling of astroglia in neurodegenerative context is multifaceted. Both astroglial atrophy with a loss of function and astroglial reactivity have been identified in virtually all the forms of neurodegenerative disorders. Astroglia may represent a novel target for therapeutic strategies aimed at preventing and possibly curing neurodegenerative diseases.

Keywords

Neurology; Neuroglia; Astroglia; Neurodegenerative diseases; Alzheimer's disease; Huntington disease; Amyotrophic lateral sclerosis

The cellular basis for neurological diseases: the central role for neuroglia

Diseases of the nervous system are the least understood and the least curable disorders known to us. This is because of an extraordinary complexity of the human nervous system, in which hundreds of billions of cells (neurones and neuroglia) connected through trillions

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of contacts (represented by chemical and electrical synapses) create the most extraordinary organ of computation, emotions and creativity. The nervous system evolved through cell diversification and cell specialisation; this resulted in the emergence of many distinct types of neurones, which are capable of generating and propagating action potentials that, in combination with the synaptic machinery, provide for fast signalling within neural networks. The second class of cells that evolved in parallel is represented by a hugely heterogeneous neuroglia, which is fully responsible for the homeostasis and defence of the nervous system. These two classes of neural cells differ in their biochemistry and physiology and yet they are combined to form nervous tissue, which functions because of continuous intimate communications between all cellular elements.

Neurological diseases can be defined as homeostatic failure. This definition highlights the fundamental role of neuroglia that protects the nervous system through multiple homeostatic mechanisms and is capable of mounting the evolutionary conserved, complex and disease-specific defensive reaction known as reactive gliosis. Although glial reactivity has been discovered almost 100 years ago (and was defined in seminal works of Pío Del Río Hortega and Wilder Penfield (Del Rio Hortega & Penfield, 1927; Del Rio-Hortega, 1932)), the potential of neuroglia in neuropathology started to be acknowledged but very recently (De Keyser et al., 2008; Parpura et al., 2012; Pekna & Pekny, 2012; Verkhratsky et al., 2012; Verkhratsky et al., 2013; Burda & Sofroniew, 2014; Verkhratsky et al., 2014c; Vardjan et al., 2015; Verkhratsky & Parpura, 2016). In this paper, we present a concise overview of the general principles of astrogliopathology and brief account for the role of astrocytes in several forms of neurodegenerative diseases.

Astroglia as a central homeostatic element of the brain

Neuroglia in the nervous system consist of several types of peripheral glia (Schwann cells of the peripheral nerves, satellite glia of peripheral ganglia, enteric glial cells and olfactory ensheathing glia) and glial cells of the central nervous system (CNS). The CNS glia is divided into microglia (cells of myeloid origin that invade the CNS very early in the development and provide for the innate immunity of the nervous tissue) and the macroglia represented by astroglia, oligodendroglia and NG2 glia (Kettenmann & Ransom, 2013; Verkhratsky & Butt, 2013). Astrocytes distributed throughout the grey and the white matter of the brain and the spinal cord are, arguably, the most heterogeneous (in form and function) type of neuroglia, responsible for virtually every homeostatic need of the CNS. The main types of astroglial cells are (i) protoplasmic astrocytes of the grey matter; (ii) fibrous astrocytes of the white matter; (iii) radial glia of the embryonic CNS; (iv) «stem» astrocytes of neurogenic niches of the subvetricular and subgranular zones; (v) velate astrocytes of the cerebellum; (vi) surface-associated astrocytes, which outline the cortical surface in the posterior prefrontal and amygdaloid cortices; (vii) interlaminar, polarised and varicose projection astrocytes which are found only in the brains of high primates and humans and functions of which remain unknown; (viii) Müller glial cells of the retina; (ix) Bergmann glial cells localised in the Purkinje neurones layer of the cerebellum; (x) tanycytes of the hypothalamus; (xi) pituicytes of the neuro-hypophysis; (xii) perivascular and marginal astrocytes, which form the glia limitans barrier at the pia mater; (xiii) ependymocytes, choroid plexus cells and retinal pigment epithelial cells. All these astroglial cells have

distinct physiological properties that are defined by their respective positions in different regions of the brain and the spinal cord; nevertheless, their common and major function is to maintain homeostasis of the CNS.

Homeostatic functions of astroglia are exceptionally diverse. For example, the radial glia act as the pluripotent progenitor that through asymmetric division gives rise to neuronal and glial precursors. In the perinatal period, characterised by a massive astrogliogenesis, astrocytes support synaptogenesis through secretion of numerous trophic factors such as trombospondins, hevin, cholesterol and apolipoprotein E. Astrocytes control the structural organisation of the nervous tissue by organising the grey matter into relatively independent neurovascular units, associated with astroglial territorial domains. Astroglial cells regulate the emergence and function of blood-brain and cerebrospinal fluid-brain barriers and form the blood-brain barrier in neurohypophysis. Astrocytes, through expression of specific transporters, regulate ion homeostasis of the CNS. In particular astrocytes are fundamental for extracellular buffering of K^+ ions that regulate neuronal γ-excitability. Astrocytes contribute to neurotransmission through regulation of turnover of neurotransmitters; astroglial cells, for example, accumulate glutamate, γ-aminobutyric acid (GABA), glycine and adenosine by specific transporters, catabolise glutamate by glutamine synthetase and adenosine by adenosine kinase, which both are expressed almost exclusively in astroglia. Astrocytes supply neurones with glutamine, which is a compulsory precursor for glutamate and GABA in neurones; inhibition of astroglial-neuronal glutamate/ GABA - glutamine shuttle inhibits both excitatory and inhibitory neurotransmission. Astrocytes regulate water transport in the CNS by aquaporine 4 water channels that are presnet only in astroglia. Astrocytes also act as the major buffering system for reactive oxygen species by releasing main anti-oxidants glutathione and ascorbic acid (for detailed account of astroglial functions and relevant references see (Iadecola & Nedergaard, 2007; Kriegstein & Alvarez-Buylla, 2009; Kimelberg & Nedergaard, 2010; Zhang & Barres, 2010; Kirischuk et al., 2012; Nedergaard & Verkhratsky, 2012; Oberheim et al., 2012; Parpura & Verkhratsky, 2012; Clarke & Barres, 2013; Kettenmann & Ransom, 2013; Verkhratsky & Butt, 2013; Verkhratsky & Nedergaard, 2014; Verkhratsky et al., 2014b; Zorec et al., 2015).

Principles of astrogliopathology

Contemporary neuropathology is dominated by the neurono-centric doctrine, which considers neurones as main substrates of disease progression. Neuronal damage or pathological neuronal processes are generally believed to be the only causes and propagators of neurological disorders. This doctrine is, nevertheless, in obvious contrast with general observation that the only cells which respond to pathological insults with complex and disease-specific reactions are neuroglia.

Neuroglial cells possess an evolutionary conserved defensive programme, the reactive gliosis, that encodes profound cellular remodelling in response to various lesions to the CNS (Pekna & Pekny, 2012; Burda & Sofroniew, 2014; Verkhratsky et al., 2014c; Verkhratsky et al., 2015). The reactive gliosis is represented by reactive astrogliosis, proliferative response of NG2 glial cells and activation of microglia; all these processes co-exist in neuropathology. Reactive astrogliosis is a complex and multistage process that produces multiple cellular

phenotypes aimed at neuroprotection and regeneration. Reactive astrocytes change their morphology, biochemistry and physiology in a disease-specific context (Zamanian et al., 2012); activated astrocytes are indispensable to contain the damage (for example, by making the glial scar), and also facilitate post-lesion regeneration (Sofroniew & Vinters, 2010; Pekna & Pekny, 2012; Burda & Sofroniew, 2014; Pekny et al., 2014).

Apart from the reactive remodelling, astrocytes may also face degeneration and atrophy with a loss of function. These changes have been identified in many chronic neurological diseases and may co-exist with astroglial reactivity, that is, several population of atrophic and reactive astrocytes may be present in the pathological tissue. Astroglial atrophy and asthenia have been observed in major neuropsychiatric, neurodevelopmental and neurodegenerative diseases (Rossi et al., 2008; Staats & Van Den Bosch, 2009; Verkhratsky et al., 2010; Rajkowska & Stockmeier, 2013; Williams et al., 2013; Verkhratsky et al., 2014a; Verkhratsky et al., 2014d; Zeidan-Chulia et al., 2014; Heneka et al., 2015). In certain diseases astroglial cells may undergo pathological remodelling, which affects their homeostatic capabilities that may contribute to pathological progression. Astroglial atrophy and pathological remodelling decrease overall homoeostatic capabilities of the CNS, and may result in a reduced synaptic coverage and hence the weakening of the synaptic transmission. Functional changes in astroglia occlude neuroprotection, and in certain conditions astrocytes may release neurotoxic factors that contribute to neuronal death.

Astrogliopathololgy can be primary or secondary. In many neurological disorders astrocytes seem to be the primary pathological target. The only hitherto known primary genetic astrogliopathology is the Alexander disease, in which astrocytes bear a sporadically mutated gene encoding glial fibrillary acidic protein (GFAP), otherwise being the main component of astroglial intermediate filament system. Expression of mutant GFAP leads to an early and profound leukomalacia (Messing et al., 2012)). Astrocytes are primary targets in different types of toxic brain lesions, for eample, poisoning with heavy metals. These heavy metals (such as mercury, lead or aluminium) are specifically accumulated by astroglia, where they disrupt astrocytic glutamate uptake, with secondary excitotoxic neuronal damage (Verkhratsky et al., 2013). Similarly, a profound inhibition of astroglial glutamate transport underlie neuronal death in Wernicke-Korsakoff encephalopathy (Hazell, 2009; Hazell et al., 2009). Astrocytes are also primary targets in hepatoencephalopathy, which arises from the liver failure with subsequent hyperammoniemia; astrocytes accumulate ammonia that interferes with glutamine synthetase, incapacitates astroglial homeostatic cascades responsible for K^+, Na^+, pH and Ca^{2+} homeostasis and induces pathological release of glutamate (Kelly et al., 2009; Haack et al., 2014; Liang et al., 2014; Montana et al., 2014). Astrocytes have also been suggested to be a primary element in addictive disorders with: the inability of astroglial cells to maintain a balance between synaptic and extra-synaptic glutamate being an important mechanism (Scofield & Kalivas, 2014). In many pathological contexts astrogliopathology is a secondary process, which represents a reaction to various insults to the nervous tissue. Reactive astrogliosis is an example of the secondary astrogliopathology that develops in many neurological diseases such as neurotrauma, stroke, infection, or later stages of neurodegeneration (Heneka et al., 2010; Burda & Sofroniew, 2014; Pekny et al., 2014). Activation of astrocytes is a heterogeneous process often specific to the particular disease; astrogliosis results in many distinct phenotypes of activated cells.

Reactive astrogliosis is fundamental for evolution and resolution of neuropathology, and extinguishing astroglial reactivity increases neuronal vulnerability, exacerbates pathological development and alters post-lesion regeneration (Burda & Sofroniew, 2014; Pekny et al., 2014).

Neurodegenerative diseases

Neurodegenerative diseases, which affect almost exclusively humans, are chronic neurological disorders that result in a progressive loss of function, structure and number of neural cells, ultimately resulting in the atrophy of the brain and profound cognitive deficits. The causes of neurodegenerative diseases may include physical, chemical or infectious trauma, genetic predisposition, metabolic deficits or a combination of a above likely with some other, yet unknown factors. Molecular and cellular mechanisms of neurodegeneration remains generally unresolved, although certain mutant genes responsible for various forms of neurodegeneration have been identified (Bekris et al., 2010; Bertram et al., 2010). Neurodegeneration is often associated with abnormal protein synthesis that results in an accumulation of pathological proteins either inside or outside the cells. These proteins are, for example, represented by β-amyloid or α-synuclein. In the extracellular space these pathological proteins often aggregate forming the cores for histopathological lesions known as senile plaques, Lewy bodies or Rosenthal fibres. These lesions are specific for various diseases and demonstrate complex morphology with regular presence of reactive astrocytes and activated microglia. In many neurodegenerative disorders the synaptic weakness, synaptic loss and neurotransmission dysbalance develop at the early stages (Terry, 2000; Knight & Verkhratsky, 2010); later in the disease progression neurones die and the brain atrophy ensues.

Astroglia in major neurodegenerative diseases

Parkinson’s disease

Astroglial contribution to Parkinson’s disease (PD) is yet to be fully described and understood. Experiments in primary cell cultures demonstrated that astrocytes are important for the protection and survival of dopaminergic neurones (Mena et al., 2002; Mena & Garcia de Yebenes, 2008). Experiments in neuronal glial co-cultures showed that astrocytes convert the dopamine precursor L-DOPA to dopamine (Mena et al., 1996). In addition, astrocytes contribute to dopamine metabolism and transport of dopamine and its precursors from the blood to the brain. Dopamine is transported into astrocytes by a large neutral amino acids transporter encoded by the SLC7A5 gene. The dopamine precursors tyrosine and L-DOPA are taken from the blood by LAT1/4F2hc complex, which is expressed in astroglia. Astrocytes may also express functional dopamine transporter DAT1/SLC6A3. L-DOPA was found to be transported also by an organic cation transporter 1, which is expressed in astrocytes. In the striatum, astrocytes provide a reservoir for L-DOPA which can be released and transported to neurones (Asanuma et al., 2014).

Amyotrophic lateral sclerosis

The specific degeneration and death of motor neurones localised in the cortex, in the brain stem and in the spinal cord are a cellular substrate of amyotrophic lateral sclerosis (ALS), which is also known as motor neurone disease or Lou Gehrig disease. Astrocytes significantly contribute to the pathophysiology of ALS; both reactive astrogliosis and astroglial degeneration with functional asthenia have been identified in this disorder. At the early stages of ALS astrocytes are affected by degeneration and many astroglial cells die by apoptosis. The degenerated astrocytes in ALS context were reported to have deficient glutamate transport, which most probably contributes to glutamate excitotoxicity and secondary neuronal death (Rossi & Volterra, 2009; Staats & Van Den Bosch, 2009; Valori et al., 2014). As the disease progresses, the dying neurones instigate astroglial reactivity; this, however, is of mild variety and never results in the scar formation. In animal models of ALS, in mice which expresses mutant human gene for superoxide dismutase 1 (hSOD1 G93A), astrodegeneration and astroglial death were found to precede neuronal death and clinical symptoms (Rossi et al., 2008). Expression of glutamate transporters was decreased in astrocytes in ALS animal models. At the same time, the genetic deletion of excitatory amino acid transporter 2 (EAAT2, also known as GLT-1 in rodents) caused death of motoneurones, thus mimicking the ALS pathological evolution (Staats & Van Den Bosch, 2009). Finally, selective silencing of the SOD1 mutant gene expression in astrocytes significantly slowed the progression of the ALS in transgenic mice (Yamanaka et al., 2008; Wang et al., 2011).

Human immunodeficiency virus-1 (HIV-1) associated dementia

The main CNS target of HIV-1 is represented by microglia. Microglial cells infected by HIV-1 undergo activation, which in turn induces secretion of pro-inflammatory and neurotoxic factors, which mediate neuronal death that result in subsequent cognitive deficits characteristic for HIV-associated dementia (HAD) (Kaul & Lipton, 2006). In HAD, both astrodegeneration and reactive astrogliosis have been identified. A significant decrease in the density of astrocytes in HAD was identified in the basal ganglia, with a correlation between the progression of cognitive impairments and the degree of astroglial death (Thompson et al., 2001). Reactive astrogliosis seems to be the most prominent in the entorhinal cortex and hippocampus of HAD patients (Vanzani et al., 2006).

Alzheimer’s disease

The Alzheimer’s disease (AD), named by Emil Kraepelin after Alois Alzheimer who identified and described the first case of early familial form of dementia (Alzheimer, 1907), is characterised by progressive loss of memory and cognitive abilities associated with specific histopathological lesions. These latter are represented by senile plaques (extracellular depositions of β-amyloid protein) and interneuronal tangles that occur due to abnormal phosphorylation of tau protein (Braak et al., 1998; Armstrong, 2009). The accepted contemporary hypothesis of the AD revolves around production and accumulation of β-amyloid protein - the β-amyloid cascade hypothesis (Korczyn, 2008; Karran et al., 2011). This hypothesis has been recently criticised (Hardy, 2009; Castellani et al., 2010; Castellani & Smith, 2011); furthermore, ~200 of clinical trials based on this hypothesis have been performed in last 2 decades and each and every one of them had failed.

There are evidence indicating that astrocytes can contribute to production as well as to degradation of β-amyloid protein. Reactive astrocytes, for example, have been shown to accumulate and degrade β-amyloid (Guenette, 2003; Nicoll & Weller, 2003). In post-mortem AD tissue β-amyloid was identified in astroglial cells from the entorhinal cortex (Nagele et al., 2003), although it was only occasionally found in astrocytes from the triple transgenic model of AD (3xTG-AD mice; (Olabarria et al., 2010)); the 3xTG-AD mouse harbours 3 mutant genes for presenelin 1, amyloid precursor protein and tau protein (Oddo et al., 2003). In transgenic mice expressing mutant amyloid precursor protein (APP), reactive astrocytes were found to express the amyloid degrading enzyme neprilysin (Apelt et al., 2003). Development of AD-related pathology may alter the ability of astrocytes to accumulate and degrade β-amyloid; cultured primary astrocytes isolated from healthy mice brain actively took up β-amyloid, whereas astrocytes isolated from mutant APP transgenic mice were unable to do so (Wyss-Coray et al., 2003).

Do astrocytes produce β-amyloid remains an open question. In the healthy brain astroglial cells do not express β-secretase and therefore are not capable of producing β-amyloid. In contrast, astrocytes exposed to chronic stress were found to express β-secretase and produce β-amyloid (Rossner et al., 2005). Astroglial expression of β-secretase was detected also in various AD mice models (Rossner et al., 2001; Heneka et al., 2005).

Reactive astrocytes (defined by the increased expression of GFAP and hypertrophic morphology) associated with senile plaques are frequently detected in the post-mortem AD tissues (Beach & McGeer, 1988; Griffin et al., 1989; Meda et al., 2001; Mrak & Griffin, 2005; Rodriguez et al., 2009). In animal models of AD reactive astroglial cells were likewise found in association with plaques (Verkhratsky et al., 2010). Hypertrophic GFAP-positive astroglial cells surrounding the plaques preserve their individual territorial domains, indicating the isomorphic astrogliosis, and there are no indications of scar formation in the context of AD. Reactive astrocytes in AD animal models show aberrant physiology; they produce spontaneous Ca^{2+} oscillations and abnormal intercellular Ca^{2+} waves (Kuchibhotla et al., 2009; Lim et al., 2014). Astroglial Ca^{2+} signalling, initiation of astrogliotic response and β-amyloid seem to be directly interconnected. Exposure of primary hippocampal cultured astrocytes as well as astrocytes in organotypic hippocampal slices to β-amyloid evokes Ca^{2+} oscillations, which result from intracellular Ca^{2+} release from the endoplasmic reticulum (ER) calcium store. The same exposure also instigated astroglial reactivity. Inhibition of the β-amyloid-induced Ca^{2+} release inhibits astrogliotic remodelling (Alberdi et al., 2013). Astrogliotic response to β-amyloid and to AD-type pathology differs very much between brain regions. In the 3xTG-AD mice, accumulation of β-amyloid induced astrogliotic response in the hippocampus, but not in the prefrontal or in the entorhinal cortices (Olabarria et al., 2010; Yeh et al., 2011; Kulijewicz-Nawrot et al., 2012). This deficit of astrogliotic response correlated with the absence of β-amyloid remodelling of Ca^{2+} signalling in the entorhinal astrocytes. At the same time exposure of hippocampal astroglia to β-amyloid substantially up-regulated the expression of main components of Ca^{2+} signalling toolkit (plasmalemmal glutamate metabotropic receptors and inositol 1,4,5 trisphosphate receptors of the ER (Grolla et al., 2013)).

At the early stages of the AD type pathology in genetic mice models substantial astroglial atrophy is generally observed (Olabarria et al., 2010; Yeh et al., 2011; Kulijewicz-Nawrot et al., 2012; Beauquis et al., 2013; Verkhratsky et al., 2014a; Verkhratsky et al., 2016). Decrease of GFAP-positive and glutamine synthetase (GS)-positive astroglial morphological profiles have been identified in several brain regions in 3xTg-AD mice (Olabarria et al., 2010; Yeh et al., 2011; Kulijewicz-Nawrot et al., 2012). This astroglial atrophy was quantified by decreased surface area and volume of GFAP/GS-positive profiles, reduced volume of cell somata and reduced number of primary processes. The total number of GFAP-positive astrocytes, however, remained stable in the hippocampus, entorhinal and prefrontal cortices of AD mice at all ages (1 – 24 month of age) (Olabarria et al., 2010; Yeh et al., 2011; Kulijewicz-Nawrot et al., 2012). The very same astroglial atrophy was also detected in astrocytes from hippocampi in a different AD animal model, the mutant APP (PDAPP-J20) mice carrying the Swedish and Indiana APP human mutations (Beauquis et al., 2013).

Emergence of atrophic astrocytes in the 3xTG-AD mouse model occurred at different time points in different brain regions (Figs. 1, 2). Significant atrophy was detected at early stages (at 1 months of age) in the entorhinal cortex; it appeared later (~ 6 months) in the prefrontal cortex and in hippocampus the atrophy become obvious only at ~9 – 12 months (Olabarria et al., 2010; Yeh et al., 2011; Kulijewicz-Nawrot et al., 2012; Verkhratsky et al., 2016). In all regions, however, astroglial atrophy preceded an the development of β-amyloid senile plaques. Incidentally, astroglial expression of mutant PS1 gene affected vesicular trafficking (Stenovec et al., 2016), which might be one of the underlying mechanism of cellular atrophy.

The atrophic morphology of astrocytes in the brains of 3xTG-AD animals possibly results in a reduced astroglial synaptic coverage, which could lead to change in synaptic strength. Astrodegeneration may also affect the neuro-vascular unit and could impact upon astroglia-dependent neuroprotection. Astrocytes are fundamental for neurotransmission by supplying neurons with glutamine that is an obligatory precursor for glutamate and GABA. Atrophy of astrocytes, therefore, may lead to deficits in the synaptic strength and may even contribute to a decrease in the number of active synapses, otherwise observed at the early stages of AD (Terry, 2000). Astroglial atrophy may also affect the brain circulation, as the deficiency in the blood flow is a characteristic feature of AD (Bell & Zlokovic, 2009). Astrocytes are central elements of neurovascular units that integrate neurones with local circulation. Astrocytes secrete various factors that mediate vasoconstriction and vasodilation by acting on pericytes or smooth muscle cells of arterioles; astrocytes also communicate with endothelial cells and support the blood-brain barrier (Zonta et al., 2003; Mulligan & MacVicar, 2004; Takano et al., 2006). Thus, an early astroglial atrophy and the later astrogliosis may contribute to vascular pathology and deficient circulation. Progression of the AD is also associated with developing metabolic deficiency, for example, in the glucose utilisation, as identified using functional brain imaging in AD patients starting from the very early stages of the disease (Mosconi et al., 2008). Exposure of cultured astrocytes to β-amyloid affects their metabolism, which may have pathological significance (Soucek et al., 2003; Allaman et al., 2010).

Huntington's disease

Huntington's disease (HD) was described by George Huntington in 1872 as a chorea-type motor disorder (Huntington, 1872). The HD is an inherited, autosomal dominant and progressive neurodegeneration associated with specific genetic aberration of the triplet nucleotide repeat cytosine-adenine-guanine (CAG), which encodes glutamine in exon 1 of the ubiquitously expressed huntingtin gene (Zuccato & Cattaneo, 2014). Expression of this mutant gene results in the synthesis of mutant huntingtin protein (mhtt), which contains an expanded polyglutamine section in the N-terminal portion; the higher is the number of glutamine repeats the more severe is the disease (Zoghbi & Orr, 2000). The mhtt mutant protein is expressed throughout the CNS, and is present in both neurones and astrocytes. Astroglial expression of mhtt results in a significant decrease in the density of astroglial plasmalemmal glutamate transporters with consequent occlusion of astroglial glutamate uptake. This decrease in astroglial expression of EAAT2/GLT-1 transporter has been detected in post-mortem human tissues and in a mouse genetic model of HD (Lievens et al., 2001; Behrens et al., 2002; Hassel et al., 2008; Faideau et al., 2010). Deficient astroglial glutamate uptake results in elevated glutamate concentration in the brain and is, arguably, the leading factor in excitotoxicity and neuronal death (Lievens et al., 2001; Shin et al., 2005; Hassel et al., 2008). Astrocytes may also contribute to glutamate excitotoxicity in HD through pathological secretion of glutamate, which was identified in astrocytes isolated from an HD animal model (Lee et al., 2013), known as BACHD mouse (Gray et al., 2008). Cultured astrocytes, prepared from the cortex of BACHD mouse demonstrated an enhanced Ca^{2+}-dependent exocytotic release of glutamate, which appeared to be the result of an increased expression of pyruvate carboxylase, an astrocyte-specific enzyme critical for de novo synthesis of glutamate. Increase in glutamate synthesis stipulated and increased glutamate content in the exocytotic vesicles. In addition, astrocytes in a different HD mouse model show deficient K^+ buffering which may further contribute to the pathogenesis of the disease (Tong et al., 2014).

Conclusions

Pathological changes in astroglia are present in all neurodegenerative diseases. These astroglial changes include astrodegeneration and astroglial atrophy with loss of function as well as astroglial reactivity. These astroglial changes are region-specific and evolve distinct temporal domains. They are responsible for abnormal CNS homeostasis and may contribute to neuronal death. Astroglia therefore may represent a novel target for therapeutic strategies aimed at preventing and possibly curing neurodegenerative diseases.

Acknowledgments

The authors' research was supported by Alzheimer's Research Trust (UK) Programme Grant (ART/ PG2004A/1) to AV and JJR; by National Institutes of Health (The Eunice Kennedy Shriver National Institute of Child Health and Human Development award HD078678) to VP; by the grants P3 310, J3 4051, J3 3632, J36790 and J3 4146 from the Slovenian Research Agency (ARRS) and the EduGlia ITN EU grant to RZ and AV; by Plan Nacional de I+D+I 2008–2011 and ISCIII-Subdirección General de Evaluación y Fomento de la investigación co-financed by FEDER (grant PI10/02738 to J.J.R and AV); by the Government of the Basque Country grants AE-2010-1-28, AEGV10/16 and GV- 2011111020 to J.J.R. AV was also supported by IKERBASQUE, by the grant (agreement from August 27 2013 № 02.B.49.21.0003) between the Ministry of Education and Science of the Russian Federation and the Lobachevsky State University of Nizhny Novgorod; by the grant of the Russian Scientific Foundation No.

14-15-00633 and by the Ministry of Education of the Russian Federation; unique identity number of the project is RFMEFI57814×0079.

References

Alberdi E, Wyssenbach A, Alberdi M, Sanchez-Gomez MV, Cavaliere F, Rodriguez JJ, Verkhratsky A, Matute C. Ca^{2+}-dependent endoplasmic reticulum stress correlates with astrogliosis in oligomeric amyloid beta-treated astrocytes and in a model of Alzheimer's disease. Aging Cell. 2013; 12:292–302. [PubMed: 23409977]

Allaman I, Gavillet M, Belanger M, Laroche T, Viertl D, Lashuel HA, Magistretti PJ. Amyloid-β aggregates cause alterations of astrocytic metabolic phenotype: impact on neuronal viability. J Neurosci. 2010; 30:3326–3338. [PubMed: 20203192]

Alzheimer A. Über eine eigenartige Erkrankung der Hirnrinde. Allg Z Psychiat Psych-Gericht Med. 1907; 64:146–148.

Apelt J, Ach K, Schliebs R. Aging-related down-regulation of neprilysin, a putative β-amyloid-degrading enzyme, in transgenic Tg2576 Alzheimerlike mouse brain is accompanied by an astroglial upregulation in the vicinity of β-amyloid plaques. Neurosci Lett. 2003; 339:183–186. [PubMed: 12633883]

Armstrong RA. The molecular biology of senile plaques and neurofibrillary tangles in Alzheimer's disease. Folia Neuropathol. 2009; 47:289–299. [PubMed: 20054780]

Asanuma M, Miyazaki I, Murakami S, Diaz-Corrales FJ, Ogawa N. Striatal Astrocytes Act as a Reservoir for L-DOPA. PloS one. 2014; 9:e106362. [PubMed: 25188235]

Beach TG, Mcgeer EG. Lamina-specific arrangement of astrocytic gliosis and senile plaques in Alzheimer's disease visual cortex. Brain Res. 1988; 463:357–361. [PubMed: 3196922]

Beauquis J, Pavia P, Pomilio C, Vinuesa A, Podlutskaya N, Galvan V, Saravia F. Environmental enrichment prevents astroglial pathological changes in the hippocampus of APP transgenic mice, model of Alzheimer's disease. Exp. Neurol. 2013; 239:28–37. [PubMed: 23022919]

Behrens PF, Franz P, Woodman B, Lindenberg KS, Landwehrmeyer GB. Impaired glutamate transport and glutamate-glutamine cycling: downstream effects of the Huntington mutation. Brain. 2002; 125:1908–1922. [PubMed: 12135980]

Bekris LM, Yu CE, Bird TD, Tsuang DW. Genetics of Alzheimer disease. Ger. Psyhiat. Neurol. 2010; 23:213–227.

Bell RD, Zlokovic BV. Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer's disease. Acta Neuropathol. 2009; 118:103–113. [PubMed: 19319544]

Bertram L, Lill CM, Tanzi RE. The genetics of Alzheimer disease: back to the future. Neuron. 2010; 68:270–281. [PubMed: 20955934]

Braak H, De Vos RA, Jansen EN, Bratzke H, Braak E. Neuropathological hallmarks of Alzheimer's and Parkinson's diseases. Prog Brain Res. 1998; 117:267–285. [PubMed: 9932414]

Burda JE, Sofroniew MV. Reactive gliosis and the multicellular response to CNS damage and disease. Neuron. 2014; 81:229–248. [PubMed: 24462092]

Castellani RJ, Rolston RK, Smith MA. Alzheimer disease. Disease-a-month : DM. 2010; 56:484–546. [PubMed: 20831921]

Castellani RJ, Smith MA. Compounding artefacts with uncertainty, and an amyloid cascade hypothesis that is 'too big to fail'. J. Pathol. 2011; 224:147–152. [PubMed: 21557219]

Clarke LE, Barres BA. Emerging roles of astrocytes in neural circuit development. Nature Rev. Neurosc. 2013; 14:311–321.

De Keyser J, Mostert JP, Koch MW. Dysfunctional astrocytes as key players in the pathogenesis of central nervous system disorders. J Neurol Sci. 2008; 267:3–16. [PubMed: 17935736]

Del Rio-Hortega, P. Microglia. In: Penfield, W., editor. Cytology and cellular pathology of the nervous system. New York: Hoeber; 1932. p. 482-534.

Del Rio Hortega P, Penfield W. Cerebral cicatrix. reaction of neuroglia and microglia to brain wounds. Johns Hopkins Hosp Bull. 1927; 41:278–303.

Faideau M, Kim J, Cormier K, Gilmore R, Welch M, Auregan G, Dufour N, Guillermier M, Brouillet E, Hantraye P, Deglon N, Ferrante RJ, Bonvento G. In vivo expression of polyglutamine-expanded

huntingtin by mouse striatal astrocytes impairs glutamate transport: a correlation with Huntington's disease subjects. Hum Mol Genet. 2010; 19:3053–3067. [PubMed: 20494921]

Gray M, Shirasaki DI, Cepeda C, Andre VM, Wilburn B, Lu XH, Tao J, Yamazaki I, Li SH, Sun YE, Li XJ, Levine MS, Yang XW. Full-length human mutant huntingtin with a stable polyglutamine repeat can elicit progressive and selective neuropathogenesis in BACHD mice. J Neurosci. 2008; 28:6182–6195. [PubMed: 18550760]

Griffin WS, Stanley LC, Ling C, White L, Macleod V, Perrot LJ, White CL 3rd, Ara-Oz C. Brain interleukin 1 and S-100 immunore-activity are elevated in Down syndrome and Alzheimer disease. Proc Natl Acad Sci U S A. 1989; 86:7611–7615. [PubMed: 2529544]

Grolla AA, Sim JA, Lim D, Rodriguez JJ, Genazzani AA, Verkhratsky A. Amyloid-β and Alzheimer's disease type pathology differentially affects the calcium signalling toolkit in astrocytes from different brain regions. Cell death & disease. 2013; 4:e623. [PubMed: 23661001]

Guenette SY. Astrocytes: a cellular player in A β clearance and degradation. Trends Mol Med. 2003; 9:279–280. [PubMed: 12900212]

Haack N, Dublin P, Rose CR. Dysbalance of astrocyte calcium under hyperammonemic conditions. PloS one. 2014; 9:e105832. [PubMed: 25153709]

Hardy J. The amyloid hypothesis for Alzheimer's disease: a critical reappraisal. J. Neurochem. 2009; 110:1129–1134. [PubMed: 19457065]

Hassel B, Tessler S, Faull RL, Emson Pc. Glutamate uptake is reduced in prefrontal cortex in Huntington's disease. Neurochem. Res. 2008; 33:232–237. [PubMed: 17726644]

Hazell AS. Astrocytes are a major target in thiamine deficiency and Wernicke's encephalopathy. Neurochem Int. 2009; 55:129–135. [PubMed: 19428817]

Hazell AS, Sheedy D, Oanea R, Aghourian M, Sun S, Jung JY, Wang D, Wang C. Loss of astrocytic glutamate transporters in Wernicke encephalopathy. Glia. 2009; 58:148–156. [PubMed: 19565658]

Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, Jacobs AH, Wyss-Coray T, TVitorica J, Ransohoff RM, Herrup K, Frautschy SA, Finsen B, Brown GC, Verkhratsky A, Yamanaka K, Koistinaho J, Latz E, Halle A, Petzold GC, Town T, Morgan D, Shinohara ML, Perry VH, Holmes C, Bazan NG, Brooks DJ, Hunot S, Joseph B, Deigendesch N, Garaschuk O, Boddeke E, Dinarello CA, Breitner JC, Cole GM, Golenbock DT, Kummer MP. Neuroinflammation in Alzheimer's disease. The Lancet Neurology. 2015; 14:388–405. [PubMed: 25792098]

Heneka MT, Rodriguez JJ, Verkhratsky A. Neuroglia in neurodegeneration. Brain Res Rev. 2010; 63:189–211. [PubMed: 19944719]

Heneka MT, Sastre M, Dumitrescu-Ozimek L, Dewachter I, Walter J, Klockgether T, Van Leuven F. Focal glial activation coincides with increased BACE1 activation and precedes amyloid plaque deposition in APPV717I transgenic mice. J Neuroinflam. 2005; 2:22.

Huntington G. On Chorea. Medical and Surgical Reporter of Philadelphia. 1872; 26:317–321.

Iadecola C, Nedergaard M. Glial regulation of the cerebral microvasculature. Nature Neurosci. 2007; 10:1369–1376. [PubMed: 17965657]

Karran E, Mercken M, De Strooper B. The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. Nature Rev Drug discovery. 2011; 10:698–712. [PubMed: 21852788]

Kaul M, Lipton SA. Mechanisms of neuronal injury and death in HIV-1 associated dementia. Current HIV Res. 2006; 4:307–318.

Kelly T, Kafitz KW, Roderigo C, Rose CR. Ammonium-evoked alterations in intracellular sodium and pH reduce glial glutamate transport activity. Glia. 2009; 57:921–934. [PubMed: 19053055]

Kettenmann, H.; Ransom, BR., editors. Neuroglia. Oxford: Oxford University Press; 2013.

Kimelberg HK, Nedergaard M. Functions of astrocytes and their potential as therapeutic targets. Neurotherapeutics. 2010; 7:338–353. [PubMed: 20880499]

Kirischuk S, Parpura V, Verkhratsky A. Sodium dynamics: another key to astroglial excitability? Trends Neurosci. 2012; 35:497–506. [PubMed: 22633141]

Knight RA, Verkhratsky A. Neurodegenerative diseases: failures in brain connectivity? Cell Death Differ. 2010; 17:1069–1070. [PubMed: 20543854]

Korczyn AD. The amyloid cascade hypothesis. Alzheimer's & dementia. 2008; 4:176–178.

Kriegstein A, Alvarez-Buylla A. The glial nature of embryonic and adult neural stem cells. Annu Rev Neurosci. 2009; 32:149–184. [PubMed: 19555289]

Kuchibhotla KV, Lattarulo CR, Hyman BT, Bacskai BJ. Synchronous hyperactivity and intercellular calcium waves in astrocytes in Alzheimer mice. Science. 2009; 323:1211–1215. [PubMed: 19251629]

Kulijewicz-Nawrot M, Verkhratsky A, Chvatal A, Sykova E, Rodriguez JJ. Astrocytic cytoskeletal atrophy in the medial prefrontal cortex of a triple transgenic mouse model of Alzheimer's disease. J. Anat. 2012; 221:252–262. [PubMed: 22738374]

Lee W, Reyes RC, Gottipati MK, Lewis K, Lesort M, Parpura V, Gray M. Enhanced Ca^{2+} -dependent glutamate release from astrocytes of the BACHD Huntington's disease mouse model. Neurobiol Dis. 2013; 58:192–199. [PubMed: 23756199]

Liang C, Du T, Zhou J, Verkhratsky A, Peng L. Ammonium increases Ca^{2+} signalling and up-regulates expression of TRPC1 gene in astrocytes in primary cultures and in the in vivo brain. Neurochem Res. 2014; 39:2127–2135. [PubMed: 25113123]

Lievens JC, Woodman B, Mahal A, Spasic-Boscovic O, Samuel D, Kerkerian-Le Goff L, Bates GP. Impaired glutamate uptake in the R6 Huntington's disease transgenic mice. Neurobiol Dis. 2001; 8:807–821. [PubMed: 11592850]

Lim D, Ronco V, Grolla AA, Verkhratsky A, Genazzani AA. Glial calcium signalling in Alzheimer's disease. Rev Physiol Biochem Pharmacol. 2014; 167:45–65. [PubMed: 24935225]

Meda L, Baron P, Scarlato G. Glial activation in Alzheimer's disease: the role of Abeta and its associated proteins. Neurobiol Aging. 2001; 22:885–893. [PubMed: 11754995]

Mena MA, Casarejos MJ, Carazo A, Paino CL, Garcia De Yebenes J. Glia conditioned medium protects fetal rat midbrain neurones in culture from L-DOPA toxicity. Neuroreport. 1996; 7:441–445. [PubMed: 8730801]

Mena MA, De Bernardo S, Casarejos MJ, Canals S, Rodriguez-Martin E. The role of astroglia on the survival of dopamine neurons. Mol Neurobiol. 2002; 25:245–263. [PubMed: 12109874]

Mena MA, Garcia De Yebenes J. Glial cells as players in parkinsonism: the «good,» the «bad,» and the «mysterious» glia. The Neuroscientist. 2008; 14:544–560. [PubMed: 19029058]

Messing A, Brenner M, Feany MB, Nedergaard M, Goldman JE. Alexander disease. J Neurosci. 2012; 32:5017–5023. [PubMed: 22496548]

Montana V, Verkhratsky A, Parpura V. Pathological role for exocytotic glutamate release from astrocytes in hepatic encephalopathy. Current Neuropharmacol. 2014; 12:324–333.

Mosconi L, Pupi A, De Leon MJ. Brain glucose hypometabolism and oxidative stress in preclinical Alzheimer's disease. Ann N Y Acad Sci. 2008; 1147:180–195. [PubMed: 19076441]

Mrak RE, Griffin WS. Glia and their cytokines in progression of neurodegeneration. Neurobiol Aging. 2005; 26:349–354. [PubMed: 15639313]

Mulligan SJ, Macvicar BA. Calcium transients in astrocyte endfeet cause cerebrovascular constrictions. Nature. 2004; 431:195–199. [PubMed: 15356633]

Nagele RG, D'Andrea MR, Lee H, Venkataraman V, Wang HY. Astrocytes accumulate A β 42 and give rise to astrocytic amyloid plaques in Alzheimer disease brains. Brain Res. 2003; 971:197–209. [PubMed: 12706236]

Nedergaard M, Verkhratsky A. Artifact versus reality--how astrocytes contribute to synaptic events. Glia. 2012; 60:1013–1023. [PubMed: 22228580]

Nicoll JA, Weller RO. A new role for astrocytes: β-amyloid homeostasis and degradation. Trends Mol Med. 2003; 9:281–282. [PubMed: 12900213]

Oberheim NA, Goldman SA, Nedergaard M. Heterogeneity of astrocytic form and function. Methods in molecular biology. 2012; 814:23–45. [PubMed: 22144298]

Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, Kayed R, Metherate R, Mattson MP, Akbari Y, Laferla FM. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular A β and synaptic dysfunction. Neuron. 2003; 39:409–421. [PubMed: 12895417]

Olabarria M, Noristani HN, Verkhratsky A, Rodriguez JJ. Concomitant astroglial atrophy and astrogliosis in a triple transgenic animal model of Alzheimer's disease. Glia. 2010; 58:831–838. [PubMed: 20140958]

Parpura V, Heneka MT, Montana V, Oliet SH, Schousboe A, Haydon PG, Stout RF Jr, Spray DC, Reichenbach A, Pannicke T, Pekny M, Pekna M, Zorec R, Verkhratsky A. Glial cells in (patho) physiology. J. Neurochem. 2012; 121:4–27. [PubMed: 22251135]

Parpura V, Verkhratsky A. Homeostatic function of astrocytes: Ca^{2+} and Na^{+} signalling. Translational neuroScience. 2012; 3:334–344. [PubMed: 23243501]

Pekna M, Pekny M. The neurobiology of brain injury. Cerebrum: the Dana forum on Brain Science. 2012; 2012:9. [PubMed: 23447795]

Pekny M, Wilhelmsson U, Pekna M. The dual role of astrocyte activation and reactive gliosis. Neurosci Lett. 2014; 565:30–38. [PubMed: 24406153]

Rajkowska G, Stockmeier CA. Astrocyte pathology in major depressive disorder: insights from human postmortem brain tissue. Current drug targets. 2013; 14:1225–1236. [PubMed: 23469922]

Rodriguez JJ, Olabarria M, Chvatal A, Verkhratsky A. Astroglia in dementia and Alzheimer's disease. Cell Death Differ. 2009; 16:378–385. [PubMed: 19057621]

Rossi D, Brambilla L, Valori CF, Roncoroni C, Crugnola A, Yokota T, Bredesen DE, Volterra A. Focal degeneration of astrocytes in amyotrophic lateral sclerosis. Cell Death Differ. 2008; 15:1691–1700. [PubMed: 18617894]

Rossi D, Volterra A. Astrocytic dysfunction: Insights on the role in neurodegeneration. Brain Res Bull. 2009; 80:224–232. [PubMed: 19631259]

Rossner S, Apelt J, Schliebs R, Perez-Polo JR, Bigl V. Neuronal and glial β-secretase (BACE) protein expression in transgenic Tg2576 mice with amyloid plaque pathology. J Neurosci Res. 2001; 64:437–446. [PubMed: 11391698]

Rossner S, Lange-Dohna C, Zeitschel U, Perez-Polo JR. Alzheimer's disease β-secretase BACE1 is not a neuron-specific enzyme. J Neurochem. 2005; 92:226–234. [PubMed: 15663471]

Scofield MD, Kalivas PW. Astrocytic dysfunction and addiction: consequences of impaired glutamate homeostasis. The Neuroscientist. 2014; 20:610–622. [PubMed: 24496610]

Shin JY, Fang ZH, Yu ZX, Wang CE, Li SH, Li XJ. Expression of mutant huntingtin in glial cells contributes to neuronal excitotoxicity. J Cell Biol. 2005; 171:1001–1012. [PubMed: 16365166]

Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. Acta Neuropathol. 2010; 119:7–35. [PubMed: 20012068]

Soucek T, Cumming R, Dargusch R, Maher P, Schubert D. The regulation of glucose metabolism by HIF-1 mediates a neuroprotective response to amyloid beta peptide. Neuron. 2003; 39:43–56. [PubMed: 12848931]

Staats KA, Van Den Bosch L. Astrocytes in amyotrophic lateral sclerosis: direct effects on motor neuron survival. J Biol Phys. 2009; 35:337–346. [PubMed: 19669429]

Stenovec M, Trkov S, LasiČ E, Terzieva S, Kreft M, RodrÍGuez Arellano JJ, Parpura V, Verkhratsky A, Zorec R. Glia. 2016; 64:317–329. [PubMed: 26462451]

Takano T, Tian GF, Peng W, Lou N, Libionka W, Han X, Nedergaard M. Astrocyte-mediated control of cerebral blood flow. Nature Neurosci. 2006; 9:260–267. [PubMed: 16388306]

Terry RD. Cell death or synaptic loss in Alzheimer disease. J Neuropathol Exp Neurol. 2000; 59:1118–1119. [PubMed: 11138931]

Thompson KA, Mcarthur JC, Wesselingh SL. Correlation between neurological progression and astrocyte apoptosis in HIV-associated dementia. Ann Neurol. 2001; 49:745–752. [PubMed: 11409426]

Tong X, Ao Y, Faas GC, Nwaobi SE, Xu J, Haustein MD, Anderson MA, Mody I, Olsen ML, Sofroniew MV, Khakh BS. Astrocyte Kir4.1 ion channel deficits contribute to neuronal dysfunction in Huntington's disease model mice. Nature Neurosci. 2014; 17:694–703. [PubMed: 24686787]

Valori CF, Brambilla L, Martorana F, Rossi D. The multifaceted role of glial cells in amyotrophic lateral sclerosis. Cellular and molecular life sciences : CMLS. 2014; 71:287–297. [PubMed: 23912896]

Vanzani MC, Iacono RF, Caccuri RL, Troncoso AR, Berria MI. Regional differences in astrocyte activation in HIV-associated dementia. Medicina (B Aires). 2006; 66:108–112. [PubMed: 16715757]

Vardjan N, Verkhratsky A, Zorec R. Pathologic potential of astrocytic vesicle traffic: new targets to treat neurologic diseases? Cell Transp. 2015; 24:599–612.

Verkhratsky, A.; Butt, AM. Glial Physiology and Pathophysiology. Chichester: Wiley-Blackwell; 2013.

Verkhratsky A, Marutle A, Rodriguez-Arellano JJ, Nordberg A. Glial Asthenia and Functional Paralysis: A New Perspective on Neurodegeneration and Alzheimer's Disease. The Neuroscientist. 2014a

Verkhratsky A, Nedergaard M. Astroglial cradle in the life of the synapse. Phil Trans Roy Soc B. 2014; 369:20130595. [PubMed: 25225089]

Verkhratsky A, Nedergaard M, Hertz L. Why are Astrocytes Important? Neurochem Res. 2014b; 40:389–401. [PubMed: 25113122]

Verkhratsky A, Olabarria M, Noristani HN, Yeh CY, Rodriguez JJ. Astrocytes in Alzheimer's disease. Neurotherapeutics. 2010; 7:399–412. [PubMed: 20880504]

Verkhratsky A, Parpura V. Astrogliopathology in neurological, neurodevelopmental and psychiatric disorders. Neurobiol Dis. 2016; 85:254–261. [PubMed: 25843667]

Verkhratsky A, Parpura V, Pekna M, Pekny M, Sofroniew M. Glia in the pathogenesis of neurodegenerative diseases. Biochem Soc Trans. 2014c; 42:1291–1301. [PubMed: 25233406]

Verkhratsky A, Rodriguez JJ, Parpura V. Astroglia in neurological diseases. Future neurology. 2013; 8:149–158. [PubMed: 23658503]

Verkhratsky A, Rodriguez JJ, Steardo L. Astrogliopathology: a central element of neuropsychiatric diseases? The Neuroscientist. 2014d; 20:576–588. [PubMed: 24301046]

Verkhratsky A, Sofroniew MV, Messing A, Delanerolle NC, Rempe D, Rodriguez JJ, Nedergaard M. Neurological diseases as primary gliopathies: a reassessment of neurocentrism. ASN neuro. 2012; 4:e00082. [PubMed: 22339481]

Verkhratsky A, Steardo L, Parpura V, Montana V. Translational potential of astrocytes in brain disorders. Prog Neurobiol. 2015

Verkhratsky A, Zorec R, Rodriguez JJ, Parpura V. Astroglia dynamics in ageing and Alzheimer's disease. Curr Opin Pharmacol. 2016; 26:74–79. [PubMed: 26515274]

Wang L, Gutmann DH, Roos RP. Astrocyte loss of mutant SOD1 delays ALS disease onset and progression in G85R transgenic mice. Hum Mol Genet. 2011; 20:286–293. [PubMed: 20962037]

Williams MR, Hampton T, Pearce RK, Hirsch SR, Ansorge O, Thom M, Maier M. Astrocyte decrease in the subgenual cingulate and callosal genu in schizophrenia. Eur Arch Psychit Clin Neurosci. 2013; 263:41–52.

Wyss-Coray T, Loike JD, Brionne TC, Lu E, Anankov R, Yan F, Silverstein SC, Husemann J. Adult mouse astrocytes degrade amyloid-β in vitro and in situ. Nat Med. 2003; 9:453–457. [PubMed: 12612547]

Yamanaka K, Chun SJ, Boillee S, Fujimori-Tonou N, Yamashita H, Gutmann DH, Takahashi R, Misawa H, Cleveland DW. Astrocytes as determinants of disease progression in inherited amyotrophic lateral sclerosis. Nature Neurosci. 2008; 11:251–253. [PubMed: 18246065]

Yeh CY, Vadhwana B, Verkhratsky A, Rodriguez JJ. Early astrocytic atrophy in the entorhinal cortex of a triple transgenic animal model of Alzheimer's disease. ASN neuro. 2011; 3:271–279. [PubMed: 22103264]

Zamanian JL, Xu L, Foo LC, Nouri N, Zhou L, Giffard RG, Barres BA. Genomic analysis of reactive astrogliosis. J Neurosci. 2012; 32:6391–6410. [PubMed: 22553043]

Zeidan-Chulia F, Salmina AB, Malinovskaya NA, Noda M, Verkhratsky A, Moreira JC. The glial perspective of autism spectrum disorders. Neurosci Biobehav Rev. 2014; 38:160–172. [PubMed: 24300694]

Zhang Y, Barres BA. Astrocyte heterogeneity: an underappreciated topic in neurobiology. Curr Opin Neurobiol. 2010; 20:588–594. [PubMed: 20655735]

Zoghbi HY, Orr HT. Glutamine repeats and neurodegeneration. Annu Rev Neurosci. 2000; 23:217–247. [PubMed: 10845064]

Zonta M, Angulo MC, Gobbo S, Rosengarten B, Hossmann KA, Pozzan T, Carmignoto G. Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation. Nature Neurosci. 2003; 6:43–50. [PubMed: 12469126]

Zorec R, Horvat A, Vardjan N, Verkhratsky A. Memory Formation Shaped by Astroglia. Front Integr Neurosci. 2015; 9:56. [PubMed: 26635551]

Zuccato C, Cattaneo E. Huntington's disease. Handbook of experimental pharmacology. 2014; 220:357–409. [PubMed: 24668480]

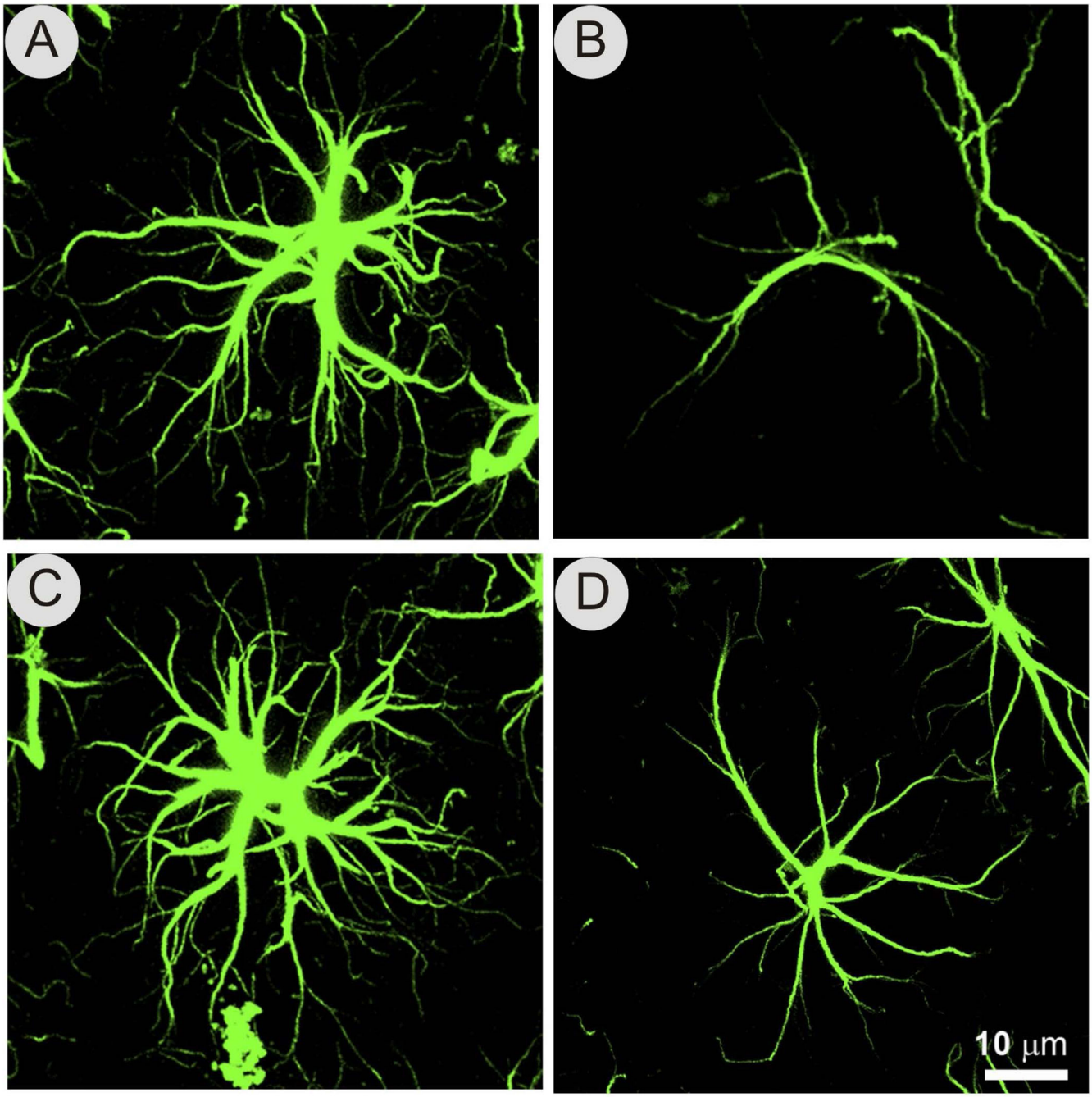

Figure 1.

Atrophic astroglia in the hippocampus of genetic mice model (the 3xTG-AD mice) of AD. A – D: High magnification microscopic images of normal astrocytes compared to the atrophic ones in dentate gyrus (A - healthy controls, B - 3xTG-AD animals); and in Cornu Ammonis area 1 or CA1 (C - healthy controls, D - 3xTG-AD animals). Modified and adapted from (Verkhratsky et al., 2014d).

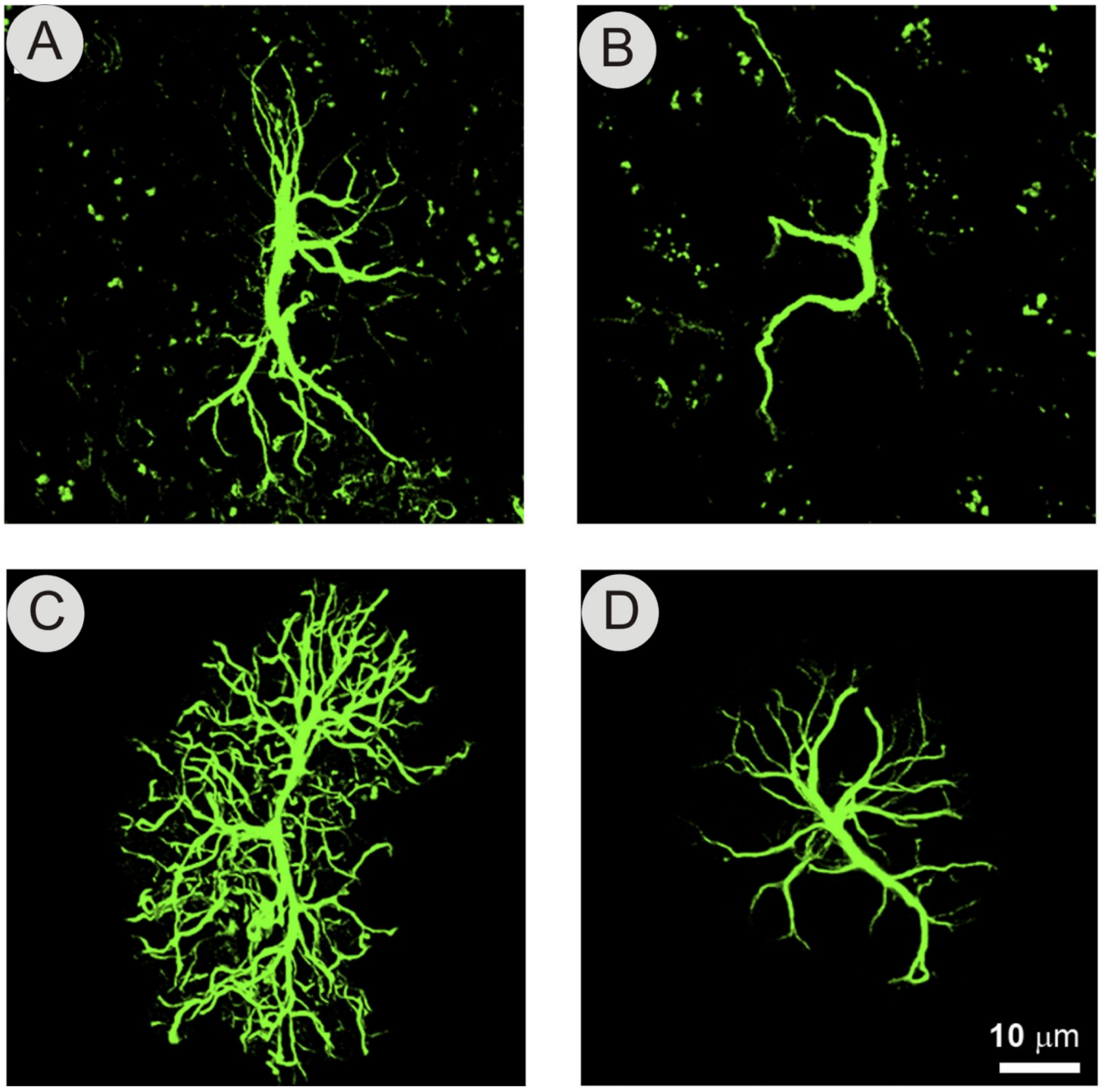

Figure 2.

Atrophic astroglia in the entorhinal and prefrontal cortex of genetic mice model (the 3xTG-AD mice) of AD. A – D: High magnification microscopic images of normal astrocytes compared to the atrophic ones in the entorhinal cortex (A - healthy controls, B - 3xTG-AD animals) and in prefrontal cortex (C - healthy controls, D - 3xTG-AD animals). Modified and adapted from (Yeh et al., 2011; Kulijewicz-Nawrot et al., 2012; Verkhratsky et al., 2014a).