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 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.,
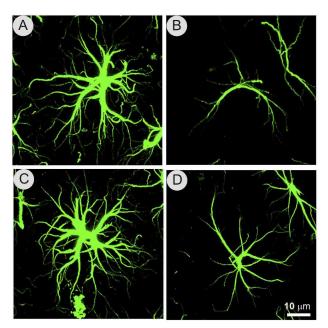

Figure 1. Atrophic astroglia in the hippocampus of genetic mice model (the 3xTG-AD mice) of AD. A - D: High magnification microscopic images of normal astrocytes compared to the atrophic ones in dentate gyrus (A - healthy controls, B - 3xTG-AD animals); and in Cornu Ammonis area 1 or CA1 (C - healthy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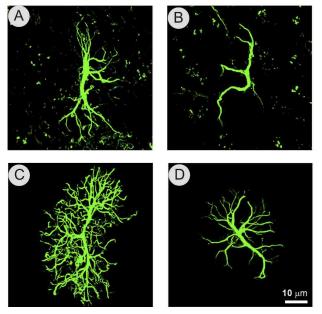

Figure 2. Atrophic astroglia in the entorhinal and prefrontal cortex of genetic mice model (the 3xTG-AD mice) of AD. A - D: High magnification microscopic images of normal astrocytes compared to the atrophic ones in the entorhinal cortex (A - healthy controls, B - 3xTG-AD animals) and in prefrontal cortex (C - healthy controls, D - 3xTG-AD animals). Modified and adapted from (Yeh et al., 2011; Kulijewicz-Nawrot et al., 2012; Verkhratsky et al., 2014a).

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 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.

Acknowledgements

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