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Astroglipathology in neurological, neurodevelopmental and psychiatric disorders

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Abstract

Astroglial cells represent a main element in the maintenance of homeostasis and providing defense to the brain. Consequently, their dysfunction underlies many, if not all, neurological, neuropsychiatric and neurodegenerative disorders. General astroglipathology is evident in diametrically opposing morpho-functional changes in astrocytes, i.e. their hypertrophy along with reactivity or atrophy with asthenia. Neurological disorders with astroglial participation can be genetic, of which Alexander disease is a primary sporadic astroglipathology, environmentally caused, such as heavy metal encephalopathies, or neurodevelopmental in origin. Astroglia also play a role in major neuropsychiatric disorders, ranging from schizophrenia to depression, as well as in additive disorders. Furthermore, astroglia contribute to neurodegenerative processes seen in amyotrophic lateral sclerosis, Alzheimer's and Huntington's diseases.

Keywords

neuroglia; astrocyte; reactive astrogliosis; neurological diseases; hepatic encephalopathy; psychiatric diseases; neurodegeneration

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Astroglia as a main element of brain homeostasis and defense

The brain and the spinal cord (which constitute the central nervous system or CNS) are composed of several types of cells that are derived from the ectoderm, i.e., the neuroepithelium (neurons and macroglia) and from other germ layers (microglia, cells of blood vessels, fibroblasts, endothelial cells etc.) (Fig. 1) (Burda and Sofroniew, 2014; Verkhatsky and Butt, 2013). These many types of cells, that differ in their structure and function, are assembled in highly complex networks coordinated by signaling molecules either released into the extracellular space (neurotransmitters, neurohormones, neuromodulators, growth factors, cytokines, trophic factors, etc.) or molecules translocated between cells using intercellular diffusion channels formed by gap junctions (Verkhatsky, 2009; Verkhatsky, 2010).

Macroglial cells of the CNS are represented by astroglia, oligodendroglia and NG2 glia, of which the latter two types are lineage-related and are mainly responsible for myelination and various forms of axonal support. Astrocytes represent cells highly heterogeneous in structure and function, which provide for fundamentals of overall homeostasis of the CNS. Conceptually, astrocytes are responsible for virtually every conceivable homeostatic task that occurs in developing and functional CNS. Astroglia are the central elements of neurogenesis and the development of the CNS (the radial glia being the pluripotent neural precursor and the scaffold for newborn neural cells migration (Kriegstein and Alvarez-Buylla, 2009)). Astrocytes are important for the structural organization of the nervous tissue (they organize the grey matter into a series of relatively independent neurovascular units), and for synaptogenesis and synaptic maturation (astroglial cells are obligatory for the formation of at least 50% of CNS synapses. They also control synapses through the secretion of multiple factors such as thrombospondins, cholesterol or neuregulins) and play a role in the formation and regulation of brain-blood and brain-cerebrospinal fluid barriers. Moreover, astrocytes regulate neurotransmitters turnover (astrocytes take up glutamate, γ -aminobutyric acid (GABA), glycine and adenosine by specific transporters, catabolize glutamate and adenosine by glutamine synthetase and adenosine kinase expressed almost solely in astroglia and supply neurons with glutamine which appears as a compulsory precursor for glutamate and GABA). They contain numerous transporters that control ion homeostasis in the CNS. Astrocytes are intimately involved in sensing brain hyperthermia and are the main component of heat stress response; they specifically upregulate the expression of the 70 kDa heat shock proteins (Hsp70). These chaperones are the primary components of the heat shock response which are expressed exclusively in neuroglia and not in neurons (Sharma, 2011). Finally, these cells are indispensable for water transport and for scavenging reactive oxygen species (as astroglia is the major source of glutathione and ascorbic acid). All these homeostatic functions of astroglia are well known and have been overviewed in numerous papers published in the past decade to which we do refer our reader (see (Clarke and Barres, 2013; Iadecola and Nedergaard, 2007; Kettenmann and Ransom, 2013; Kimelberg and Nedergaard, 2010; Nedergaard and Verkhatsky, 2012; Oberheim et al., 2012; Parpura et al., 2012; Zhang and Barres, 2010)).

Homeostatic capabilities of astroglia are of paramount importance for CNS function in physiological conditions, and naturally they are critical for brain response to pathological

insults of any etiology. The disease being homeostatic failure develops when homeostatic reserves are exhausted, and neurological diseases critically depend on the capability of astrocytes to maintain homeostasis of the CNS. Furthermore, astrocytes are endowed with evolutionarily conserved program, which is activated in pathological conditions, the program of reactive astrogliosis which remodels cellular biochemistry, structure and function in an attempt to contain the pathological developments. The pathological potential of astrocytes is not, however, limited to their reactivity; in many types of neuropathology astrodegeneration and loss of astroglial function acquire serious pathological significance.

General gliopathology: Reactivity and atrophy

Pathological changes in the CNS affect all cell types (Fig. 1) and lead to a complex and disease-specific remodeling of cellular networks. Already in early histopathological studies, performed at the beginning of the 20th century, both progressive (which we now refer to as reactive) and regressive (atrophic and degenerative) remodeling changes have been documented (for the early history of gliopathology see for example (Glees, 1955; Kettenmann and Verkhatsky, 2008)). All types of neuroglial cells affected by the insult undergo complex and multifaceted changes leading to an appearance of numerous new “reactive” phenotypes. The reactive gliotic response is represented by reactive astrogliosis, reactive activation of NG2 cells, reactive remodeling of oligodendroglia (which is partly manifested as Wallerian degeneration) and the activation of microglia. Neuropathology is also associated with glial atrophy, loss of function or pathological remodeling, which generally reduces homeostatic and defensive capabilities of these cells and may permit or mediate various forms of neurotoxicity. Complex neuropathological changes that occur in glial cells inspired a reassessment of neuron-centrism in neuropathology (Barres, 2008; Molofsky et al., 2012; Nedergaard et al., 2010; Thrane et al., 2014; Verkhatsky et al., 2014b; Verkhatsky et al., 2014c; Verkhatsky et al., 2012).

Reactive astrogliosis has been regarded as a purely pathological, detrimental reaction that exacerbates the neuropathological progression, although this point of view gradually yields to a modern concept that regards astrogliotic response as an intrinsically defensive and protective metamorphosis aimed at the preservation and regeneration of the neural tissue (Pekna and Pekny, 2012; Pekny et al., 2014; Sofroniew, 2009; Sofroniew and Vinters, 2010; Verkhatsky et al., 2012). Generally, astroglial reactivity is defined as astrocytic hypertrophy and proliferation that goes along with an up-regulation of cytoskeletal components such as glial fibrillary acidic protein (GFAP), vimentin or nestin (Pekny and Nilsson, 2005; Sofroniew, 2009; Sofroniew and Vinters, 2010). Increased GFAP expression and corresponding enlargement of GFAP-positive cellular profiles are considered as a specific marker for astrogliotic response.

In reality, reactive astrogliosis has much more complex biological nature, affecting the expression of hundreds of genes that in turn modify numerous enzymatic and signaling cascades in pathology-related context. All these modifications provide diversified outcomes, which for example, include improved neuroprotection through increasing homeostatic and trophic support of stressed neurons, formation of an astroglial scar that isolates the lesioned area from the rest of the brain, facilitation of the post-lesion regeneration or reconstruction

of the compromised blood–brain barrier. Suppression of reactive astrogliosis exacerbates damage to the CNS and impedes regeneration (Robel et al., 2011; Sofroniew and Vinters, 2010). Reactive astrocytes are heterogeneous in their form and function; in isomorphic gliosis, for example, astrocytes become hypertrophic, albeit their domain organization remains preserved; whereas in anisomorphic gliosis, astroglial hypertrophy and proliferation result in the disruption of astroglial domains and in the formation of a glial scar. Isomorphic astrogliosis is fully reversible and promotes neurite growth and synaptogenesis and the regeneration of neuronal networks. Anisomorphic reactive astrocytes secrete chondroitin and keratin, which promote the formation of the scar that denies contacts between the damaged area and the rest of the CNS (Sofroniew, 2009; Sofroniew and Vinters, 2010; Verkhatsky et al., 2014b; Verkhatsky et al., 2012).

In many neuropathological conditions, however, astrocytes undergo atrophy and functional asthenia which affect their homeostatic and protective capabilities. Astrodegeneration and asthenia can be the only features of neuropathology or can coexist with reactive responses. Astrodegeneration and loss of the ability to sequester glutamate are manifested at the early stages of amyotrophic lateral sclerosis (ALS), and may be one of the key mechanisms of neurotoxicity (Rossi and Volterra, 2009; Staats and Van Den Bosch, 2009). Selective silencing of mutant superoxide dismutase 1 (which is directly associated with some forms of familial ALS) expression in astrocytes delays the disease progression (Wang et al., 2011). Similarly, atrophic changes and functional asthenia of astrocytes are observed in neurodegenerative pathologies such as Alzheimer's or Huntington's diseases (AD and HD) (Lee et al., 2013; Verkhatsky et al., 2014a; Verkhatsky et al., 2010). Astroglial asthenia and atrophy have also been observed in major neuropsychiatric disorders such as schizophrenia and major depressive disorders (Hercher et al., 2009; Rajkowska et al., 2002; Rajkowska and Stockmeier, 2013; Verkhatsky et al., 2014d; Williams et al., 2013).

Astroglia in neurological diseases

Alexander Disease

Alexander disease (AxD), described by W. Stewart Alexander in 1949 (Alexander, 1949), is a primary genetic astrogliopathy caused by the sporadic mutation of GFAP-encoding gene (Messing et al., 2012; Messing et al., 2010). This is a rare (with a prevalence of 1 in 2.7 million people (Yoshida et al., 2011)) and usually fatal disease that strikes infants and young adults. Expression of mutant GFAP results in remarkable deficits in white matter formation, AxD being in essence a leukodystrophy. The histological hallmark of AxD is the presence of Rosenthal fibers in astrocytes, which are cytoplasmic inclusions, formed by GFAP in association with stress proteins (such as α - and β -crystallin and heat shock protein 27). In AxD, astrocytes undergo pathological remodeling, which is manifested by the disruption of blood-brain barrier with Rosenthal fibers being concentrated around the endfeet, increased oxidative stress, decrease astroglial neuroprotection, and compromised astroglial glutamate uptake.

Neurodevelopmental disorders

Autism spectrum disorders (ASD) define a widely heterogeneous group of neurodevelopmental diseases, which are broadly characterized by aberrant social interaction, and restrictive patterns of behaviors (Quaak et al., 2013). Although the pathogenic mechanisms of ASD are poorly defined, it is safe to assume that the abnormal formation of neuronal networks and aberrant/disbalanced neurotransmission play an important, if not the key, role. There are also numerous indications that oxidative stress either *in utero* or in early postnatal period may be involved in pathological networking. Astrocytes are fundamental for synaptogenesis and neuronal connectivity as well as for scavenging reactive oxygen species, and hence they naturally can contribute to ASD evolution. Increased astroglial reactivity, as judged by elevated GFAP expression, has been identified in autistic brains (Zeidan-Chulia et al., 2014). Astrocytes are also known to be the primary target for numerous agents, including heavy metals, chlorinated acetates, fluoxetine, ethanol, all of which affect astroglial metabolism and homeostatic capabilities (Kreft et al., 2012; Verkhatsky et al., 2013); all these agents are thought to be associated risk factors to ASD and astroglia may mediate the link (Zeidan-Chulia et al., 2014). Incidentally, the expression of connexin43, that mediates astroglial gap junctional connectivity, was increased in ASD patients (Fatemi et al., 2008a). Moreover, viral infection during pregnancy in mice affects the expression of Cx43 in astrocytes in parallel to other long-term changes in brain protein expression associated with altered brain development (Fatemi et al., 2008b).

Down syndrome (DS) is a genetic disorder associated with trisomy of chromosome 21; as far as the nervous system is concerned, it is manifested by a neurodevelopmental failure characterized by severe mental retardation. Histopathology of DS has a semblance to Alzheimer's disease with the occurrence of both neuritic plaques and intraneuronal tangles (Wisniewski et al., 1985). On a micro-architectural level, DS is characterized by severe reduction in the number of neurons and glia in cortical structures (by 30 – 40% - (Karlsen and Pakkenberg, 2011)). DS astrocytes, derived from fibroblasts obtained from DS patients through reprogramming into pluripotent stem cells which subsequently were differentiated in astroglia, were more susceptible to oxidative stress. In addition, these DS astrocytes were deficient in supporting synaptogenesis and neuronal maturation *in vitro*; minocyclin, a broad-spectrum tetracycline antibiotic excreting neuroprotective effects independent of its anti-inflammatory properties (Maier et al., 2007), was able to partially restore these supportive astroglial functions (Chen et al., 2014).

Fragile X syndrome (also known as Martin–Bell syndrome, or Escalante's syndrome), is a neurodevelopmental disorder associated with the expression of Fragile X mental retardation protein; this protein is considered to be the most common single-gene cause of autism and mental retardation. The Fragile X mental retardation protein is expressed in astrocytes as well as in neurons. It turned out that astrocytes isolated from genetic mouse model of fragile X syndrome fail to adequately support neurons in co-culture (Jacobs and Doering, 2010) and delayed neuronal maturation and development (Jacobs et al., 2010).

Neurotrauma

Reactive astrogliosis is the primary response of astrocytes to neurotrauma both in experimental animals and humans (Laird et al., 2008). Activation of astroglial program occurs within 1 to 2 days after the focal traumatic brain injury and it ultimately results in the formation of glial scar that in turn limits the damage (Burda and Sofroniew, 2014). Inhibition of astroglial response (for example by the administration of ganciclovir that becomes toxic following conversion with thymidine kinase) suppresses the formation of glial scar and exacerbates traumatic pathology (Sofroniew, 2005). Reactive astrocytes are also ultimately required for post traumatic repair of blood brain barrier and the regeneration of neuronal networks (Laird et al., 2008). At the same time, traumatic brain injury may initiate loss of astroglial function, which for example is represented by the down-regulation of astrocytic glutamate transporters observed in rodents and in humans (Rao et al., 1998, Beschoner et al., 2007). This down-regulation results in the suppression of glial ability to contain extracellular glutamate and hence exacerbates glutamate excitotoxicity.

Stroke

It is generally acknowledged that astrocytes are substantially more ischemia-resistant than neurons and oligodendrocytes and that astrocytes may survive in conditions of limited blood supply, characteristic for penumbra surrounding the core of the ischemic infarction. These surviving astrocytes undergo gliotic activation and are instrumental for neuroprotection and post-ischemic regeneration (Takano et al., 2009; Zhao and Rempe, 2010). Astroglial neuroprotection includes the removal of excess glutamate, control over K^+ concentration in the interstitium, supplying stressed neurons with lactate (which astrocytes produce in the course of glycolysis) and scavenging reactive oxygen species by releasing glutathione and ascorbic acid. In the absence of astroglia, the vulnerability of neurons to ischemia is greatly increased in the *in vitro* settings (Tanaka et al., 1999). Reactive astrocytes surrounding the ischemic core form the glial scar, establishing a barrier between the damaged and surviving tissue. At the same time, astrocytes contribute to neurotoxicity; in conditions of metabolic stress, astroglial cells could release glutamate and ATP via plasmalemmal channels and by exocytosis thus exacerbating excitotoxicity. Astroglial anaerobic glycolysis can increase acidosis (and hence addition of glucose to the ischemic tissue can exacerbate the damage) and finally astrocytes can cause the death of neurons distant to the initial ischemic lesion through propagating aberrant Ca^{2+} waves causing the release of glutamate and other neurotoxic factors (Lin et al., 1998). Astrocytes thus define, to a very great extent, the survival (or death) of cells in penumbra and hence define infarction progression and neurological deficit.

Heavy metal toxic encephalopathies

Astrocytes appear as the main target in toxic encephalopathies caused by environmental exposure to heavy metals, such as manganese, lead, aluminum or methylmercury (this latter also known as Minamata disease). This is primarily due to the fact that astrocytes selectively accumulate metal ions because of the expression of numerous plasmalemmal transporters, with some of them being designed for metal ions transportation (zinc and iron being the most notable examples). Accumulation of heavy metals by astrocytes impairs both the

expression and function of glutamate transporters, thus compromising the ability of astrocytes to remove glutamate (Struys-Ponsar et al., 2000; Suarez-Fernandez et al., 1999; Verkhatsky et al., 2013; Yin et al., 2007). This in turn leads to the deficient glutamate turnover and the accumulation of glutamate in the extracellular space with ensuing excitotoxicity and neuronal damage. Of note, impairment of astroglial glutamate transport is rather common in pathological remodeling of astroglia and is prominent in numerous neuropathological conditions.

Hyperammonemia encephalopathy

Toxic encephalopathies caused by an increased level of blood ammonium develop in conditions of urea cycle deficiencies, such as in Reye's syndrome, or (most frequently) following a liver failure (hepatic encephalopathy). They are characterized by polymorphic mental and behavioral manifestations, such as confusion, forgetfulness, irritability as well as alterations of consciousness represented by lethargy, somnolence and, in the terminal stages, coma associated with brain edema that causes death (Ede and Williams, 1986; Felipo, 2013; Link et al., 2012; Rama Rao et al., 2014). Detoxification of ammonium in the brain is one of the many functions of astroglia; ammonia is metabolized by glutamine synthetase, an astroglia-specific enzyme (Albrecht et al., 2010; Norenberg, 1987; Rose et al., 2013). The overload of glutamine synthetase pathway and the occlusion of normal glutamate-glutamine processing was, for a long time, considered to be the primary and the only pathological mechanism of hyperammonemia-induced brain damage (Brusilow et al., 2010; Butterworth, 2011; Rama Rao and Norenberg, 2014). Recent data, however, indicates much more complex molecular pathogenesis, i.e. exposure to increased ammonium decreases the expression of $K_{ir}4.1$ channels in astrocytes and compromises CNS K^+ homeostasis (Obara-Michlewska et al., 2014; Rangroo Thrane et al., 2013), affects the expression of Ca^{2+} channels and deregulates Ca^{2+} signaling and Ca^{2+} homeostasis (Haack et al., 2014; Liang et al., 2014), causes pathological elevations in astroglial cytosolic Na^+ , impairs astroglial transport of H^+ hence affecting pH homeostasis (Kelly et al., 2009; Kelly and Rose, 2010) and triggers pathological glutamate release from astrocytes (Montana et al., 2014). Furthermore, the chronic exposure of astrocytes to ammonium impairs astroglial secretion of thrombospondin-1, which may negatively affect synaptogenesis (Jayakumar et al., 2014). All in all, hyperammonemia causes a rapid loss of astroglial homeostatic capabilities, which result in similarly rapid and severe neurological symptoms, rapid deterioration of CNS and death.

Astroglia in neuropsychiatric diseases

Wernicke's encephalopathy and Korsakoff psychosis

Wernicke's encephalopathy is a severe neurodegeneration which is often linked to Korsakoff syndrome, the latter being manifested by ante- and retrograde amnesia and confabulations; both develop as a result of thiamine deficiency and are related to alcoholism (Korsakoff, 1889; Wernicke, 1881 – 1883). At a cellular level, Wernicke encephalopathy could be considered as a primary astrogliopathy, the leading mechanism being associated with severe (60 – 70%) down-regulation of astroglial glutamate transporters EAAT1 and EAAT 2. Incidentally, the very similar down-regulation of the same transporters occurs in

the beriberi disease, which is a form of nutritional thiamine deficiency (Hazell, 2009; Hazell et al., 2009).

Schizophrenia

According to contemporary views, the abnormal connectivity in neural cellular networks and the overall misbalance of neurotransmission with a primary impairment of glutamatergic transmission could be one of the leading pathological mechanisms of schizophrenia (Laruelle, 2014; Muller and Schwarz, 2006; Rubinov and Bullmore, 2013; Schmitt et al., 2011). Astrocytes are central for both synaptogenesis and the maintenance of glutamatergic transmission and hence their contribution to schizophrenia has been receiving an increased attention (Bernstein et al., 2015; Kondziella et al., 2007; Sanacora and Banasr, 2013; Verkhatsky et al., 2014d; Xia et al., 2014). The number of main types of neuroglia, the oligodendrocytes and astrocytes, is generally decreased in the schizophrenic brain, with some regional variations (Xia et al., 2014). There are no signs of reactive astrogliosis in schizophrenia (Rajkowska et al., 2002; Rajkowska et al., 1998; Schnieder and Dwork, 2011; Williams et al., 2013). The decrease in astrocyte numbers is also paralleled by functional deficits. In particular, the expression levels of glutamate transporters EAAT1 and EAAT2 are declined in the parahippocampal region and in the dorsolateral prefrontal cortex; the EAAT2 expression was also decreased in the prefrontal cortex in patients with metabotropic glutamate receptor 3 gene (*GRM3*) haplotype linked to the high-risk of schizophrenia (Spangaro et al., 2012; Takahashi and Sakurai, 2013). There is also evidence of impaired metabolism of D-serine, a neuromodulator of the N-methyl D-aspartate (NMDA) type glutamate receptor, both in neurons and in astrocytes of the schizophrenic brain (Martineau et al., 2014). Moreover, there seems to be a link between schizophrenia and D-serine producing enzyme, serine racemase (Bendikov et al., 2007; Labrie et al., 2009); for example, the expression of mutant Disrupted-In-Schizophrenia-1 (*DISC1*) gene in astrocytes results in a decreased production of D-serine (Ma et al., 2013). Selective overexpression of the stress protein heme oxygenase-1 in astrocytes induces multiple aberrations in the brain, which includes oxidative stress, increased α -synuclein expression, increased serotonin and dopamine levels in basal ganglia, etc. All these multiple changes result in a schizophrenia-like phenotype (Song et al., 2012).

Finally, astroglia and schizophrenic pathological phenotype are directly linked through kynurenic acid. This acid is produced by the degradation of tryptophan catalyzed by kynurenine aminotransferase II (KAT II), which is expressed almost exclusively in astroglia (Guidetti et al., 2007). Kynurenic acid is an endogenous antagonist of NMDA and $\alpha 7$ nicotinic receptors and may serve as a regulator of various cognitive functions (Schwarcz and Hunter, 2007). One of the forms of schizophrenia, resulting from protozoan infection seems to be specifically associated with kynurenic acid. Namely, *Toxoplasma gondii* selectively infects astroglial cells and an increased production and secretion of kynurenic acid seems to be responsible for an increased risk of schizophrenia development in infected patients (Schwarcz and Hunter, 2007; Wilson and Hunter, 2004).

Major depressive disorder

Astrocytes are affected in the major depressive disorder (MDD). The number of astrocytes (defined by Nissl staining of their nuclei or by staining with GFAP antibodies) is reduced in many regions of the brain of MDD post-mortem tissues; these regions include the prefrontal cortex, orbitofrontal cortex, subgenual cortex, anterior cingulate cortex, hippocampus and amygdala (Rajkowska and Stockmeier, 2013). Similarly, the reduced GFAP reactivity and the number of GFAP positive astrocytes were observed in various animal models of chronic stress (Braun et al., 2009; Czeh et al., 2006). The MDD and chronic stress were also leading to a decreased expression of astroglial specific homeostatic molecules such as aquaporin 4, connexins, plasmalemmal glutamate transporters and glutamine synthetase (Barley et al., 2009; Bernard et al., 2011; Rajkowska and Stockmeier, 2013; Sequeira et al., 2009). A decrease in components of glutamate-glutamine shuttle, in particular, can be instrumental for the generalized imbalance of neurotransmission observed in MDD.

Addictive disorders

Astroglia may also be connected with the pathogenesis of various types of addictive disorders. In the post-mortem brains, a significant decrease in astrocytic numbers and morphological fragmentation of astrocytes, probably indicative of degenerative changes, have been documented (Büttner and Weis, 2006; Miguel-Hidalgo, 2009). At the same time an increase in GFAP expression and astroglial reactivity was also described in human brain samples and in various animal models of drug abuse and addiction (Armstrong et al., 2004; Fattore et al., 2002; Oehmichen et al., 1996; Suarez et al., 2000; Weber et al., 2013). The glial atrophy/degeneration and glial reactivity may reflect the stage of the disease. In the brains of patients with short-lasting alcoholic dependence the density of astrocytes decreased and their morphology was atrophic, whereas subjects with a longer history of addiction had increased GFAP expression and astrocytic numbers (Miguel-Hidalgo et al., 2006; Miguel-Hidalgo et al., 2002; Skuja et al., 2012). Moreover, both types of astroglial changes may coexist. In post-mortem tissues of alcoholic patients, both enlarged astrocytes and brain areas almost completely devoid of GFAP-positive cells have been observed (Cullen and Halliday, 1994; Miguel-Hidalgo, 2005). Deficits in astroglial control over glutamate seem to be the main functional change in astroglia in addictive disorders. Here, the expression of plasmalemmal glutamate transporter EAAT2 (which removes extracellular glutamate from the synaptic cleft) and plasmalemmal glutamate/cystine antiporter/exchanger Xc⁻ (which releases glutamate predominantly in the extrasynaptic regions) are decreased; there is an increase in overall glutamate concentration in the extracellular space, perhaps indicating a preferential reduction in EAAT2 expression and larger impediment of the glutamate removal (as opposed to a lesser decrease in the release of glutamate due to a reduction in the system Xc⁻ exchanger) making this neurotransmitter to accumulate in the extracellular space (Moussawi et al., 2011). This imbalance may be related to the pathogenesis of addictive disorders.

Astroglia in neurodegeneration

Amyotrophic lateral sclerosis

There is increasing evidence for pathological potential, and possibly a key pathogenesis role, played by astroglia in amyotrophic lateral sclerosis (ALS, also known as motor neuron disease or Lou Gehrig's disease in memory of a baseball player who suffered and died from this pathology in 1941). In transgenic animal model of ALS (that express a human mutated gene for superoxide dismutase 1, hSOD1, linked to a family form of the disease), the degeneration of astrocytes and their pathological remodeling revolving around decreased expression of glutamate transporters and decreased capability to contain glutamate excitotoxicity occur before neuronal changes. Decreased homeostatic capacity of astrocytes seem to be responsible for neuronal death; silencing of hSOD1 gene in astrocytes partially restores their function and delays ALS progression (Rossi et al., 2008; Rossi and Volterra, 2009; Valori et al., 2014; Yamanaka et al., 2008). In addition, genetic deletion of EAAT2/GLT-1 glutamate transporter in mice astrocytes mimicked the symptoms of experimental ALS (Staats and Van Den Bosch, 2009).

Alzheimer's disease

Alzheimer's disease (AD), so named by Emil Kraepelin, a German psychiatrist and the founder of modern scientific psychiatry, psychopharmacology and psychiatric genetics, in 1910 (Kraepelin, 1910) to recognize clinical observations of his pupil Alois Alzheimer (Alzheimer, 1907). AD exists in two distinct forms, the inherited family form and the sporadic form, the latter accounting for the absolute majority (arguably > 99%) of morbidity. The main pathological feature of the AD is a progressive atrophy of brain tissue that is the substrate for developing severe dementia; at the histopathological level, AD is characterized by the abundant presence of senile plaques representing extracellular deposits of β -amyloid protein and intra-neuronal accumulation of abnormal tau-protein filaments, known as neurofibrillary tangles (Braak et al., 1998; Selkoe, 2001).

AD astroglia, studied in transgenic animal models of the familial form(s) of the disease, undergo both atrophy (which is region specific and appears at the early stages of the pathology) and, at the later stages, reactivity, which possibly is triggered by extracellular deposition of β -amyloid; reactive astrocytes are generally associated with senile plaques (Fuller et al., 2009; Olabarria et al., 2010; Rodriguez and Verkhatsky, 2011). The reactive astrocytes, however, may appear before the formation of plaques, as, for example, was observed in the grey matter of the transgenic mice over-expressing the London mutant of amyloid precursor protein, APP [V717I]. These reactive astrocytes were grouped together, releasing pro-inflammatory factors and had an up-regulated expression of inducible nitric oxide synthetase (iNOS); it has been suggested that these groups of reactive astroglia marked spots where senile plaques are subsequently formed (Heneka et al., 2005).

Similarly, astrocytes characterized by morphological atrophy (decrease in GFAP, S100 β and glutamine synthetase antibodies stained profiles) appear before the formation of senile plaques in the hippocampus, entorhinal cortex and prefrontal cortex of transgenic AD mice (Beauquis et al., 2013; Beauquis et al., 2014; Kulijewicz-Nawrot et al., 2012; Olabarria et

al., 2010; Yeh et al., 2011). Astroglial atrophy in the entorhinal and prefrontal cortices develops much earlier than in the hippocampus of triple transgenic (3xTG) AD mice. Importantly, in these regions astrocytes do not mount reactive response to extracellular β -amyloid (Kulijewicz-Nawrot et al., 2012; Yeh et al., 2011), which may underlie higher vulnerability of these parts of the brain to AD pathology (Verkhatsky et al., 2014a). The mechanism of deficient reactivity may involve impaired Ca^{2+} signaling in astroglial cells. In the entorhinal cortex, for example, β -amyloid failed to up-regulate metabotropic (G-protein coupled) Ca^{2+} signaling toolkit; however, this up-regulation was evident in the hippocampus (Grolla et al., 2013; Lim et al., 2014). Calcium signals associated with metabotropic pathway and specifically with inositol 1,4,5-trisphosphate-mediated Ca^{2+} release from the endoplasmic reticulum store are instrumental for triggering reactive astrogliosis (Alberdi et al., 2013; Kanemaru et al., 2013); weakening of this cascade may account for a deficient gliotic response in astrocytes from certain brain regions. Astroglial atrophy may be a part of AD pathogenesis as reduced astroglial homeostatic capabilities as well as reduced astrocytic synaptic coverage may affect synaptic transmission, synaptic connectivity and neuronal survival, thus contributing to cognitive deficits and atrophy of the brain (Verkhatsky et al., 2010).

Huntington's disease

Huntington's disease (HD) described by George Huntington, an American physician, in 1872 as a chorea-type motor disorder (Huntington, 1872) is an inherited, autosomal dominant and progressive neurodegeneration. At the very core of the disease lies a genetic aberration associated with the triplet nucleotide repeat cytosine-adenine-guanine (CAG), which encodes glutamine, in exon 1 of the widely expressed huntingtin gene (The Huntington's Disease Collaborative Research Group, 1993). The mutant gene, when expressed, results in the synthesis of mutant huntingtin protein (mhtt) containing an expanded polyglutamine section in its N-terminal portion; the higher the number of CAG repeats, the more severe is the disease progression (Zoghbi and Orr, 2000).

The mutant protein mhtt is expressed in neurons and in astroglia (Singhrao et al., 1998) and this expression affects astroglial function. Similar to many other neurodegenerative conditions the prominent pathological feature of astrocytes in R6/2 HD mouse is deficient glutamate uptake, caused by reduced expression of the EAAT2/GLT1 glutamate transporter (Behrens et al., 2002; Faideau et al., 2010; Hassel et al., 2008; Lievens et al., 2001). This astroglial homeostatic failure causes an increase in glutamate concentration in striatum and possibly other regions of the brain and could be a leading factor in neurotoxicity and ensuing neurodegeneration (Hassel et al., 2008; Lievens et al., 2001; Shin et al., 2005). Astrocytes further contribute to glutamate excitotoxicity in HD by augmented glutamate release. Increased secretion of glutamate from astroglia reflects augmented Ca^{2+} -dependent exocytosis as directly demonstrated in astrocytes isolated from an HD animal model (Lee et al., 2013). This particular model, known as BACHD mouse, contains full-length human mhtt with 97 polyglutamines encoded by a modified huntingtin transgene on a human Bacterial Artificial Chromosome (BAC) (Gray et al., 2008). Astrocytes isolated from the cortex of BACHD mouse and kept in culture demonstrate enhanced Ca^{2+} -dependent exocytotic release of glutamate, which appeared to be the result of an increased expression of pyruvate

carboxylase, the critical enzyme for glutamate *de novo* synthesis. This increased availability of cytosolic glutamate for accumulation into appropriate vesicles and, consequentially, increased glutamate release from astroglia. Astroglial homeostatic deficiency in R6/2 and Q175 HD mice is also manifested by a remarkable decrease of K^+ buffering, associated with decreased expression of $K_{ir}4.1$ K^+ channels (Tong et al., 2014). In conclusion, the HD affects astroglial homeostatic reserve, which can be an important component in neurotoxicity and neurodegeneration.

Conclusions

The intent of this review was to summarize up to date information of the role of astroglia in pathology, in particular that of neurological, including neurodevelopmental, neuropsychiatric and neurodegenerative disorders. We outline possible molecular entities within astroglia that are likely underpinnings of the cause, initiation and/or progression of various disorders. It is abundantly clear that astroglia may represent a site for novel therapeutic targets for medical intervention. However, it is still not apparent how basic research discoveries can be brought into the clinical settings, i.e. how to achieve bench to bed translation. For instance, we can identify a single amino acid mutation in GFAP as a cause of Alexander disease. Furthermore, we can posit a therapeutic approach to silence the mutated gene and deliver the normal gene instead. However, the uncomfortable truth is that the practicality of implementing such treatment in human medicine at present, while within the reach, is still not procured. Inevitably, future multi-faceted endeavors would yield success. We predict, however, that this task will require a colossal collaborative effort between basic and translational scientists, clinicians, industrial partners and legislature.

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Highlights

Astroglial cells represent a main element in the maintenance of the brain homeostasis

Astroglial dysfunction underlies many brain disorders

Astroglipathology in neurological, neurodevelopmental and psychiatric disorders

Astroglipathy can be evident in morpho-functional changes

Figure 1. Multicellular nature of the pathological response of the CNS tissue

The brain and the spinal cord cellular networks are composed of various cell types that include neural cells (i.e. the posterity of ectodermal neuroepithelial cells) represented by neurons, astrocytes, oligodendrocytes and NG2 glia, and cells of mesodermal origin (microglial cells, smooth muscle cells of the blood vessels, blood cells, fibroblasts and pericytes, although the precise origin of the latter remain somewhat controversial). Pathological responses of the CNS involve all these cell types in a disease-specific fashion and may be manifested in reactive responses of astrocytes, NG2 cells and microglia, in pathological remodeling of oligodendrocytes, in atrophic changes of all these cells, in CNS tissue invasion by peripheral monocytes, etc. The specificity of cellular response defines the evolution, progression and resolution of neuropathological conditions. See details in the text.