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Research report

Human astrocytes in the diseased brain

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ABSTRACT

Astrocytes are key active elements of the brain that contribute to information processing. They not only provide neurons with metabolic and structural support, but also regulate neurogenesis and brain wiring. Furthermore, astrocytes modulate synaptic activity and plasticity in part by controlling the extracellular space volume, as well as ion and neurotransmitter homeostasis. These findings, together with the discovery that human astrocytes display contrasting characteristics with their rodent counterparts, point to a role for astrocytes in higher cognitive functions. Dysfunction of astrocytes can thereby induce major alterations in neuronal functions, contributing to the pathogenesis of several brain disorders. In this review we summarize the current knowledge on the structural and functional alterations occurring in astrocytes from the human brain in pathological conditions such as epilepsy, primary tumours, Alzheimer's disease, major depressive disorder and Down syndrome. Compelling evidence thus shows that dysregulations of astrocyte functions and interplay with neurons contribute to the development and progression of various neurological diseases. Targeting astrocytes is thus a promising alternative approach that could contribute to the development of novel and effective therapies to treat brain disorders.

1. Introduction

Astrocytes are active dynamic signalling players of the central nervous system (CNS). Over the past 25 years it has become clear that astrocytes participate to a variety of essential physiological processes in the healthy brain. Indeed, far from being merely passive cells providing structural support to neurons, astrocytes are now viewed as crucial active and dynamic elements of the brain circuitry: they participate in formation and maturation of synapses, receptor trafficking, control of the homeostasis of ions and energy metabolites and clearance of neurotransmitters. They also regulate the extracellular space volume and modulate the moment-to-moment synaptic plasticity (Araque et al., 2014; Dallérac and Rouach, 2016). Many studies have shown their contribution to information processing and memory formation in the brain, thereby pointing to a role of astrocytes in higher integrated brain functions. Dynamic bidirectional signalling between astrocytes and neurons has mainly been reported in experimental animal models. Recent data however show that such reciprocal signalling also occurs in the human brain. Astrocytes from human brain tissue indeed exhibit Ca^{2+}-based "intrinsic excitability" and can respond to synaptically-released neurotransmitters (Navarrete et al., 2012). Furthermore, morphological, genomic and functional studies have revealed that human astrocytes display specific characteristics compared to the rodent counterpart (Miller et al., 2010; Oberheim et al., 2006, 2009; Zhang et al., 2016; Zheng et al., 2015). Human astrocytes display a remarkable morphological diversity according to cortical layers, being larger and more complex than those of rodents; furthermore, they exhibit a high expression of proteins involved in Ca^{2+} signalling and propagate Ca^{2+} waves at much faster velocities than their rodent counterparts (Bazargani and Attwell, 2016; Oberheim et al., 2009). Altogether, these findings support the idea that in the human brain, astrocytes may play a crucial role underlying higher cognitive functions. Alterations in astrocyte physiological roles have thus been hypothesized to contribute to cerebral pathology. Indeed, as early as in the 19th century, several neuropathologists such as Alzheimer, Fromman and Nissl, already envisioned a role for glia in brain diseases. Nonetheless, since the beginning of the 20th century the concept that neurological diseases result primarily from neuronal dysfunction dominated.

Abbreviations: Aβ, amyloid Beta; AQP, aquaporin; AD, Alzheimer's disease; CNS, central nervous system; Cx, connexin; DS, Down syndrome; GJ, gap junction; GFAP, glial fibrillary acidic protein; GS, glutamine synthetase; HS, hippocampal sclerosis; IP3R2, inositol triphosphate receptor 2; MDD, major depressive disorder; MTLE, mesial temporal lobe epilepsy; mGluR5, metabotropic glutamate receptor 5.

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However, this neurocentric paradigm did not systematically lead to prominent advances in therapies for brain diseases. Such diseases indeed still remain the most complicated to understand and treat. Growing evidence from analysis of post-mortem or surgically resected human tissues and from animal models of CNS pathologies indicate that astroglial dysfunctions contribute to the pathogenesis of several neurological and psychiatric disorders (Halassa et al., 2007; Rossi and Volterra, 2009).

In this review we focus on human-specific astroglial changes in some frequent neurological disorders, such as epilepsy, brain tumours, Alzheimer's disease, major depressive disorder and Down syndrome.

2. Astrogliosis as a hallmark of brain diseases

A common feature and pathological hallmark of several CNS diseases is reactive astrogliosis (Fig. 1). It consists of a finely graded continuum of molecular, cellular and functional changes in astrocytes in response to CNS injuries; these alterations vary according to the severity of the disease (Anderson et al., 2014; Eddleston and Mucke, 1993) and are regulated through inter- and intracellular signalling molecules in a context-specific manner (Sofroniew, 2009). In mild or moderate astrogliosis, which is generally associated with mild trauma or located in areas at a certain distance from CNS lesions, astrocytic proliferation is almost absent. Variable increased glial fibrillary acidic protein (GFAP) expression has also been observed, together with cell body and process hypertrophy, which is not altering astrocyte organization into individual distinct domains (Wilhelmsson et al., 2006). Furthermore, other proteins are up-regulated in reactive astrocytes, such as copper-zinc superoxide dismutase, glutathione peroxidase or metallothionein. Moderate astrogliosis also results in expression of inducible nitric oxide synthase and release of trophic factors and cytokines, including tumour necrosis factors α and β, interleukins and interferons (Chen and Swanson, 2003). In mild or moderate forms, reactive astrogliosis exhibits the potential for resolution, if the initial triggering insult resolves or is removed; in this case, cells return to a condition similar to that observed in healthy tissue (Sofroniew, 2009). On the contrary, near focal lesions, infections or neurodegenerative areas severe diffuse astrogliosis is characterized by enhanced astrocytic proliferation. Molecular factors promoting proliferation of reactive astrocytes are not completely characterized, but a role for epidermal growth factor, fibroblast growth factor, endothelin 1, ATP, lipopolysaccharide and nitric oxide has been identified (Gadea et al., 2008; Levison et al., 2000; Neary and Zimmermann, 2009; Sofroniew and Vinters, 2010). This enhanced astrocytic proliferation causes intermingling and overlapping of neighbouring astrocytic processes, which disrupts individual astrocyte domains. In some cases, this potent astrocytic reaction can drive the formation of a compact glial scar (Fig. 1). Such scar is characterized by astrocyte interaction with different cell types and is mainly formed along the borders of severe tissue damage, necrosis, tumours, chronic neurodegeneration, infection or inflammatory infiltration (Sofroniew, 2009; Sofroniew and Vinters, 2010). These structural changes are long-lasting and persist after the resolution of the triggering insult (Sofroniew, 2009). Moreover, mature glial scars act as barriers to inflammatory cells to protect surrounding healthy tissue from nearby areas of intense inflammation. Reactive astrocytes can also protect CNS cells and tissue by uptaking excitotoxic glutamate, producing glutathione against oxidative stress, degrading amyloid β peptides, regulating extracellular space volume and ion balance, facilitating blood brain barrier repair and regulating CNS inflammation. Nevertheless, growing evidence also shows that reactive astrocytes can contribute to or be the primary source of CNS physiopathology. Reactive astrocytes from glial scars can indeed synthesize collagen and sulphate proteoglycans, which prevent axon regeneration (Chen and Swanson, 2003). In addition, alteration of the physiological functions of astrocytes resulting from genetic mutations contribute to brain disorders such as Alexander's disease and amyotrophic lateral sclerosis (Brenner et al., 2001; Nagai et al., 2007). These opposite effects of reactive astrocytes thus point to a dual function of astrogliosis (Sofroniew, 2009; Sofroniew and Vinters, 2010).

3. Epilepsy

Epilepsy is one of the most prevalent neurological diseases affecting 1% of the world population (World Health Organisation, 2016, http://www.who.int/en/). It is characterized by repetitively recurrent seizures, which disrupt normal brain functions and can damage the brain and worsen pre-existing neurological deficits. Contrary to the traditional view assuming that epileptic activity is generated exclusively in and by neurons, an astrocytic basis for epilepsy has been proposed (Tian et al., 2005). Moreover, investigations on specimens from mesial temporal lobe epilepsy (MTLE) patients have identified changes in astrocytic channels and receptors (Fig. 2a–b), thus suggesting that astrocyte dysfunction can participate in hyper-excitation, neurotoxicity and seizure spreading, in addition to established neurogenic mechanisms.

3.1. Epilepsy-associated astrogliosis

Reactive astrogliosis is present in almost all forms of epilepsy, but it is most notable in presence of hippocampal sclerosis (HS), which is often associated with MTLE and other epilepsy syndromes (Thom, 2014). Indeed, besides a severe loss of principal neurons observed in CA1 and CA3 and granule cell dispersion, HS is characterized by a chronic and fibrillary gliosis in CA1 and radial gliosis in the dentate gyrus, where the length of GFAP$^+$ fibres is directly correlated with the degree of cell dispersion in the dentate gyrus (Fahrner et al., 2007). Furthermore, in HS, together with increased conventional GFAP expression, a novel GFAP isoform has been identified in small multinucleate CA1 and CA4 astrocytes, GFAP-γ, which is speculated to regulate astrocyte size and motility (Martinian et al., 2009). Whether HS is a primary cause of epilepsy or the result of repeated epileptic seizures is still controversial. Even if the prevailing view tends to consider HS as a secondary consequence of epilepsy, experimental data on surgical samples and autoptic tissues suggest that HS aetiology is multifactorial. Febrile seizures, genetic susceptibility, alterations of hippocampal development, head injuries, infections and inflammatory and neurodevelopmental factors have indeed been identified as predisposing elements to HS development (Sendrowski and Sobaniec, 2013; Thom, 2014; Walker, 2015).

3.2. Kir channels and K^+ homeostasis

It is well known that astrocytes are key players in the regulation of extracellular K^+ ($[K^+]_o$), which can transiently accumulate during prolonged neuronal activity and cause neuronal depolarization and hyper-excitability if uncompensated (Heinemann and Lux, 1977). $[K^+]_o$ homeostatic control is performed by K^+ uptake and by spatial K^+ buffering: while the former is mediated by glial and neuronal Na,K-ATPase or Na-K-Cl cotransporters, the latter is driven by the difference between the glial syncytium negative membrane potential and the local K^+ equilibrium potential. This results in redistribution of K^+ from sites of high neuronal activity to sites of lower $[K^+]_o$ through gap junction (GJ)-connected astrocytic networks (Orkand et al., 1966; Walz, 2000). This peculiar astrocytic property is mainly mediated by Kir4.1 K^+ channels,