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Role of Astrocytes in Neurodegenerative Diseases

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1. Introduction

The past several decades have given rise to many important discoveries and novel insights into the role of astrocytes in normal brain function and disease, firmly establishing concepts that describe the dynamic and reciprocal signaling networks between astrocytes, neurons and other cell types.

Brain aging, overt any neurodegenerative state, leads to inflammation, oxidative stress and cell death. Neurons are more susceptible to injury than astrocytes, as they have fewer antioxidant mechanisms and are therefore prone to excitotoxicity (Swanson *et al.,* 2004). Both normally and with aging, astrocytes support neurons by providing antioxidant protection, substrates for neuronal metabolism via neurovascular coupling, and glutamate clearance. Although astrocytes are generally more resilient than neurons, severe damage also results in astrocyte dysfunction, leading to increased neuronal death (Nedergaard & Dirnagl, 2005). Therefore, many recent efforts have focused on the astrocyte-neuron interaction and how astrocyte function can be improved to enhance neuronal support and survival (Swanson *et al.,* 2004). A growing body of data demonstrates that astrocytes play a multifaceted and complex role in the response to neuropathologies, including neurodegenerative, as they have potential to both enhance neuronal survival and regeneration and contribute to further injury (Sofroniew, 2000, 2009; Sofroniew & Vinters, 2010). Because of the diverse nature and complex biology of these cells, and the limited number of studies to date, their role in neurodegeneration deserves further study.

It is likely that diminished astrocytes function throughout the neurodegenerative process is a prominent determinant of both neuronal survival as well as survival of the entire organism (Shibata & Kobayashi, 2008). In this chapter we provide a brief overview of the pathophysiological events underlying brain aging, and in neurodegenerative diseases, and discusses how these events affect astrocytes response to these chronic neuropathologies, such as Alzheimer's AD and Parkinson´s PD diseases, Amyotrophic Lateral Syndrome (ALS), and Multiple Sclerosis (MS).

2. Astrocytes function in the brain

Astrocytes are the most common cell type in mammalian brain. Glial fibrillary acidic protein (GFAP) and vimentin (Vim) constitute intermediate filaments (known also as nanofilaments) as part of the cytoskeleton in astrocytes. Reactive gliosis is a response of astrocytes to a variety of brain insults that is characterized by hypertrophy of the cell bodies and processes, altered gene expression, increase in the expression of GFAP, Vim and the calcium binding protein S100β (Ridet *et al.,* 1997), and proliferation that may likely occur in some neurodegenerative diseases (Sofroniew, 2009; Sofroniew & Vinters, 2010). In contrast, because reactive astrocytes are ubiquitous in aged central nervous system (CNS) tissue, they are often regarded as uniformly harmful, provoking inflammation, releasing cytotoxins and chemokines that serve no purpose but to inhibit axonal regeneration and increase damage. The wide range of activities that astrocytes can exhibit *in vitro* contributes to uncertainty over whether these cells exert beneficial or detrimental effects after CNS degeneration. For example, potential protective effects could be provided by glutamate uptake and neurotrophin release, while potential detrimental effects might be caused by the release of inflammatory cytokines and cytotoxic radicals. Little information has been available on the roles played by reactive astrocytes in the response to experimental models of neurodegenerative diseases *in vivo.* For instance, aged astrocytes exhibit an elevated content of GFAP and of S100β (Barreto *et al.,* 2009; Nichols, 1999). Use of oligonucleotide arrays has yielded the first profile of gene expression from the aging brain of mice and evidence that aging seems to be associated with an inflammatory response and oxidative stress both in neocortex, hippocampus and in cerebellum (Lee *et al.,* 2000; Zeier *et al.,* 2011), with parallels to human neurodegenerative disorders. GFAP is also one of the genes that undergoes a twofold increase in expression. Thus, the GFAP increases of the aged astrocytes may be the result of a response to the inflammatory and oxidative state of the aging brain. Indeed, better comprehension of the features that distinguish a normal, "healthy" old brain from a brain that is at an early stage of a neurodegenerative disease is a key aspect in developing treatments.

It is interesting to note that one of the characteristics of astrocytes in the aging brain – the number of astrocytes – is increased by ~20% (Peinado *et al.,* 1998; Pilegaard & Ladefoged, 1996; Rozovsky *et al.,* 1998; Salminen *et al.,* 2011). This response has been compared with reactive gliosis in response to injured or damaged neurons during aging. However, an alternative explanation is that increased number of astrocytes in the aging brain is required to provide the same level of neuroprotection that is present in the brain of a young animal.

One hallmark of the cellular response to brain aging, and in neurodegenerative states, is a rapid, dramatic increase in damaging free radicals, including nitric oxide (NO), superoxide, and peroxynitrite (Shibata & Kobayashi, 2008). On the other hand, astrocytes produce the beneficial antioxidants glutathione, superoxide dismutases (SODs 1, 2 and 3), and ascorbate (Figure 1, Anderson & Swanson, 2000; Dringen, 2000; Dringen *et al.,* 2000; Lindenau *et al.,* 2000; Sims *et al.,* 2004). Interestingly, neurons cocultured with astrocyte exhibit higher levels of glutathione compared with neurons cultured alone (Giordano *et al.,* 2009), suggesting that astrocytes provide additional antioxidant defense to neurons (Slemmer *et al.,* 2008). Similarly, astrocytes upregulate HO-1 (heme-oxygenase 1, Figure 2), a 32 kDa stress protein that degrades heme to biliverdin, free iron and carbon monoxide. Although the upregulation of this enzyme has been previously reported to confer neuroprotection following various brain insults (Beschorner *et al.,* 2000; Chen *et al.,* 2000; Espada *et al.,* 2010;

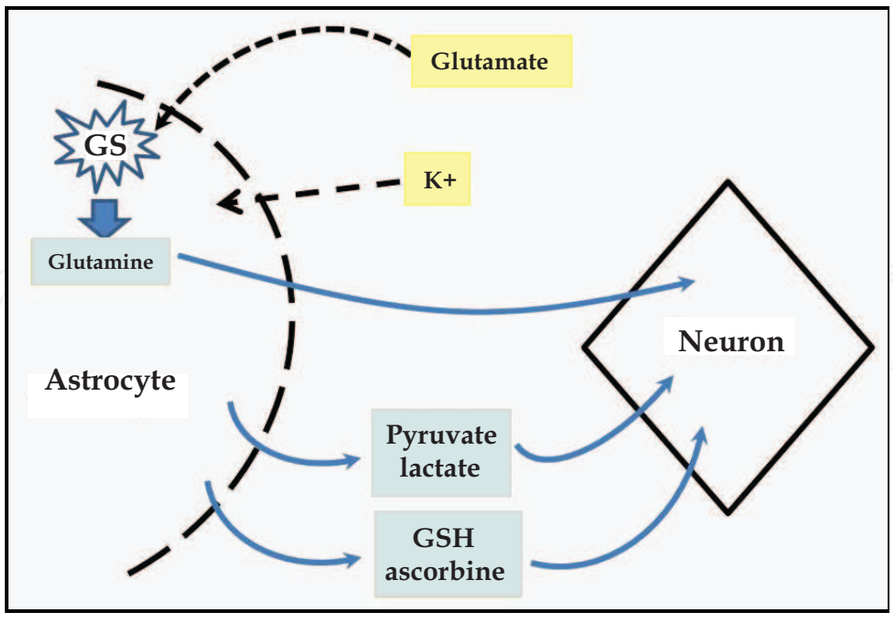

Fig. 1. Mechanisms of astrocyte support of neurons in the normal brain. Antioxidant defence includes release of glutathione and ascorbate. Regulation of extracellular levels of ions and neurotransmitters, especially K^+ and glutamate, strongly influence neuronal excitability. Elevated extracellular K^+ triggers astrocyte glycolysis and enhances lactate and pyruvate release which support neuronal metabolism. Sodium dependent glutamate uptake by astrocytes activates the Na^+/K^+ ATPase, stimulating glycolytic activity and production of lactate. Astrocytes and neurons are also coupled by the glutamate-glutamine cycle. Astrocytes take up glutamate, convert it to glutamine, release glutamine to the extracellular space where it is taken up by neurons and used to synthesize glutamate to replenishment the neurotransmitter pool. Any deregulation of these mechanisms, as a common situation in some neurodegenerative diseases, will likely influence neuronal survival

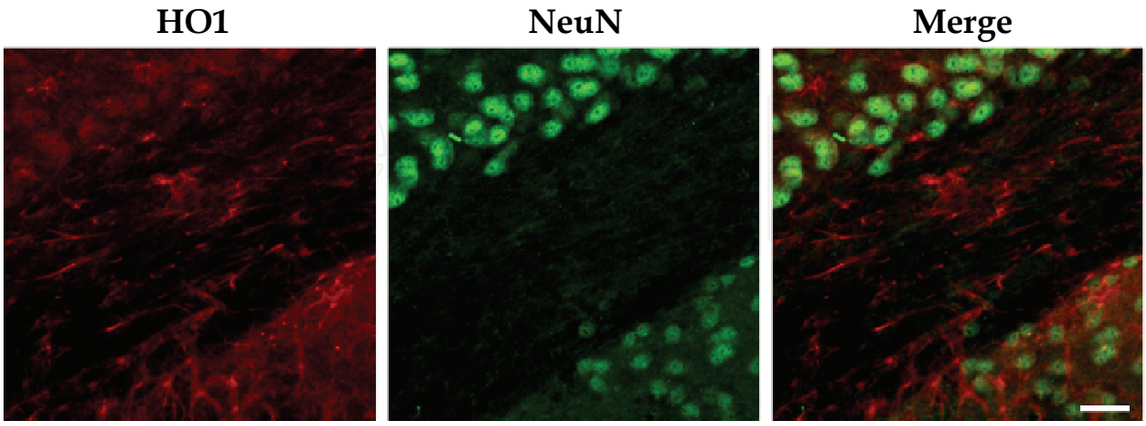

Fig. 2. Astrocytic HO-1 expression in corpus callosum. Immunostaining for HO-1 and NeuN (neuronal marker) was carried out in free floating brain sections of 3 months-old naïve male mice. Morphologically, HO-1 is expressed in shaped-like astrocytes, and does not seem to be expressed by neurons. Scale bar, 50 µm

Imuta *et al.,* 2007; Ku *et al.,* 2006; Le *et al.,* 1999; Takeda *et al.,* 2000), its overproduction in astrocytes may contribute to iron overload and mitochondrial insufficiency, characteristic of some neurodegenerative disorders (Fernandez-Checa *et al.,* 2010; Serviddio *et al.,* 2011). HO-1 is expressed by approximately 86% (Schipper *et al.,* 1995) and 77.1% (Schipper *et al.,* 1998) of GFAP-positive astrocytes in AD and PD, respectively, suggesting a possible role in the pathogenesis of these neurodegenerative diseases.

Control of energy metabolism is also controlled by astrocytes in the CNS. When astrocytes take up extracellular glutamate as a result of neuronal activity, the Na^+/ K^+-ATPase and AMPA signaling trigger astrocyte uptake of glucose from the blood, as astrocytic endfeet contact capillaries (Caesar *et al.,* 2008; Magistretti, 2006). The glucose is then made into lactate, a substrate for neuronal energy, to further "fuel" active neurons (Magistretti & Pellerin, 1999; Figure 1). As mentioned above, astrocytes produce glutathione. In addition to its antioxidant properties, glutathione is the enzyme needed for the conversion of methylglyoxal, a toxic by-product of metabolism, into D-lactate by glyoxalase 1 (Cliffe & Waley, 1961). Although the role of astrocyte metabolism is relatively well-established in normal tissues, the role of astrocyte metabolism maintenance with aging and in neurodegenerative diseases is less clear (Bartnik-Olson *et al.,* 2010; Bentzer *et al.,* 2000; Floyd & Lyeth, 2007).

Astrocytes are also key players in the production and regulation of neurotransmitters, antioxidant production, potassium uptake, energy metabolism and neurovascular coupling in the CNS. Notably, astrocytes make glutamine, the precursor for the neurotransmitters glutamate and GABA, from glucose (Zou *et al.,* 2010). In addition to providing the precursors for neurotransmitters, one important role of astrocytes in the normal brain is to take up glutamate using the glutamate transporters GLAST and GLT-1 (Anderson & Swanson, 2000; Romera *et al.,* 2004; Schousboe & Waagepetersen, 2006), as excess glutamate leads to cell death via excitotoxicity (Tilleux & Hermans, 2007).

Astrocytes regulate neuronal activation by extracellular potassium uptake, and proper maintenance of ion gradients, such as potassium, as an important mechanism for regulating cell volume in both normal and pathological conditions (Jayakumar & Norenberg, 2010; Lambert & Oberwinkler, 2005; Lang *et al.,* 1998; Obara *et al.,* 2008). Indeed, astrocytes upregulate glucose transporters in order to provide energy to dying neuronal cells (Floyd & Lyeth, 2007; Scafidi *et al.,* 2009; Yi & Hazell, 2006,) suggesting that astrocytes are necessary for improvement in chronic neurodegenerative diseases energy metabolism. In summary, astrocytes are important producers of antioxidants in the normal CNS, and astrocytic production of these molecules after brain injury may enhance neuronal survival and protect astrocyte function.

Astrocytes are critical in the development and/or maintenance of blood-brain barrier characteristics (Gordon *et al.,* 2007; Koehler *et al.,* 2009). Astrocytes are arranged in non-overlapping spatial domains (Bushong *et al.,* 2002; Halassa *et al.,* 2007), but coupled to each other in a syncytial network (Haydon & Carmignoto, 2006). Since one astrocyte maintains contacts with approximately 160,000 synapses (Bushong *et al.,* 2002), this cell population is well positioned to integrate neuronal activity and link neuronal activity to the vascular network (Ransom *et al.,* 2003).

Astrocytes terminal processes are also known as "endfeet" cover 99% of the abluminal vascular surface of capillaries, intracerebral arterioles, and venules (Simard *et al.,* 2003). The extent of contact between endfeet and penetrating and pial arterioles remains unclear. Pial arterioles and arteries lying free in the subarachnoid space are not covered (Jones, 1970).

Nevertheless, much of the pial circulation is in contact with the glia-limitans, a de-facto extension of astrocytic processes (Kontos *et al.,* 1971; Xu *et al.,* 2004). This domain organization has been proposed as being the key linking element of the neuronal–(astrocyte)–vascular unit (Volterra & Meldolesi, 2005). For example, working with neocortical slices, Zonta et al. (Zonta *et al.,* 2003) demonstrated that electrical stimulation of neuronal processes raises intracellular Ca^{2+} levels in astrocytic endfeet and leads to a slowly developing dilatation of local intracerebral arterioles. Additionally, electrical stimulation of individual astrocytes had the same effect. Since this initial report, several investigators observed a vascular response in conjunction with an elevation of intracellular Ca^{2+} levels in astrocytic endfeet. However, these studies reported inconsistent vascular responses ranging from vasorelaxation to vasodilatation or the combination of both (Gordon *et al.,* 2007; Iadecola & Nedergaard, 2007). Mediators implicated in this mechanism are vasoactive metabolites of the cyclooxygenase or cytochrome P450 ω-hydroxylase pathways. All of these studies were performed in brain slices in which the vessels are lacking in intraluminal pressure. This might account for disparate results. In vivo analysis with two-photon laser scanning microscopy revealed that increases of astrocytic Ca^{2+} by photolysis of caged Ca^{2+} evoked a vasodilatation of cortical arterioles (Takano *et al.,* 2006). This interaction between the vessel and the endfeet appeared to be mediated by metabolites of the COX-1 pathway, because inhibitors of nitric oxide synthetase (NOS), COX-2, p450 epoxygenases, and adenosine receptor antagonists had no effect. These and other studies strongly implicate a role for astrocytes in cerebral blood flow regulation during neuronal activation (Haydon & Carmignoto, 2006).

It is important to point that some, if not all, of these astrocytic functions may likely be altered or reduced in neurodegenerative states (Rossi & Volterra, 2009). The role of astrocytes in various neurodegenerative diseases will briefly be discussed more thoroughly below, specifically looking at their involvement during the pathologic processes of Alzheimer´s and Parkinson diseases, Amyotrophic Lateral Syndrome (ALS) and Multiple Sclerosis.

3. Astrocytes dysfunction in neurodegenerative diseases

Neurodegenerative diseases represent a heterogeneous group of disorders affecting the nervous system. In most instances, they affect adults, their causes are unknown, and progression is relentless. Some are genetic, but most are sporadic. They involve all parts of the nervous system, although the cerebral cortex and the basal ganglia are the most frequent loci of pathology. The historical classification of neurodegenerative diseases, based on clinical and pathological characteristics, is imperfect. New classifications are rather based on molecular determinants. Contrary to common belief, it is now recognized that neurodegenerative disorders are multisystemic, even if specific neuronal pathways are more affected than others. The death of astrocytes and specific types of neurons in neurodegenerative diseases is provoked, not by a single pathogenic factor, but rather by a cascade of multiple deleterious molecular and cellular events as described earlier.

3.1 Oxidative stress and neurodegeneration

Mitochondria are central neuronal organelles that play a vital role in neuronal life and death. Both mitochondrial dysfunction and proper function are essential components in neurodegeneration. Further elucidation of the mechanisms of interaction between

mitochondria and neuronal death will allow better description of the pathogenesis of neurodegenerative diseases and provide potential targets for therapeutic intervention.

One of the hallmarks of various neurodegenerative and neuroinflammatory disorders is oxidative stress-induced CNS damage. Similarly, the natural aging process per se is associated with increased oxidative stress (Figure 3). Such oxidative stress can damage lipids, proteins and nucleic acids of cells and power-house mitochondria causing cell death in assorted cell types including astrocytes and neurons. However, astrocytes having high levels of anti-oxidant enzymes (glutathione peroxidase, catalase, glutathione reductase, and superoxide dismutase) and antioxidants (glutathione and ascorbic acid) try to absorb reactive oxygen species (O2 =, O2 −, and OH.) and reactive nitrogen species (NO, ONOO−), maintain redox homeostasis and defend the insulted CNS (Chen & Swanson, 2003; Dringen & Hirrlinger, 2003; Wilson, 1997). In addition, astrocytes also scavenge detrimental

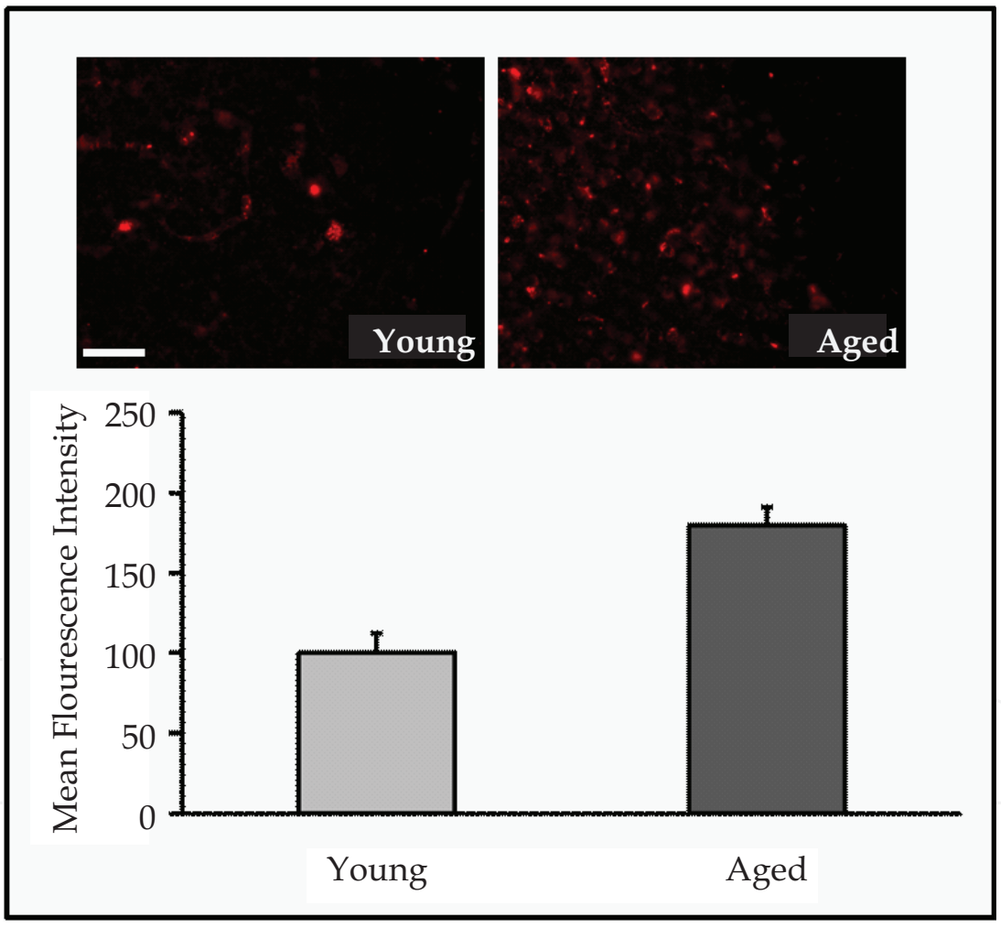

Fig. 3. Increased oxidative stress production in the normal aged brain. 3- or 18-months naïve old male mice were sacrificed and 40 µm brain sections were stained for 4-Hydroxynonenal (4-HNE), a marker of lipid peroxidation. Mean Fluorescence intensity assessed by ImageJ program showed that aged animals, overt any pathological condition, had an increased expression of 4-HNE in cortical layers II-III, compared to young mice. 3 sections/animal for 4 animals were analyzed in each condition. Data are represented as Means ± SEM. Scale bar, 100 µm

molecules such as glutamate, produced during synaptic transmission through neurons (Hertz & Zielke, 2004). This is, perhaps, the most common astrocytic dysfunction that likely occurs in some neurodegenerative states.

Astrocytes react to various neurodegenerative insults rapidly, leading to vigorous astrogliosis. This reactive gliosis is associated with alteration in morphology and structure of activated astrocytes along with its functional characteristics (Eddleston & Mucke, 1993). The astrocytic processes construct a bushy network surrounding the injury site, thus secluding the affected part from the rest of the CNS area. Subsequently, astrogliosis has been implicated in the pathogenesis of a variety of chronic neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease, Amyotrophic Lateral Syndrome (ALS), acute traumatic brain injury, stroke, and neuroinflammatory brain diseases (Axelsson *et al.*, 2011; Ciesielska *et al.,* 2009; Garcia-Matas *et al.,* 2010; Heales *et al.,* 2004; Li *et al.,* 2011; Simpson *et al.,* 2010; Sofroniew, 2000).

3.2 Alzheimer´s disease

AD is characterized clinically by cognitive loss in two or more domains, including memory, language, calculations, orientation and judgment; the loss must be of sufficient severity to cause social or occupational disability. These clinical features are the result of neuronal death and dysfunction in the cerebral cortex, entorhinal area, hippocampus, ventral striatum and basal forebrain, eventually resulting in severe dementia. Pathologically, the two hallmark findings of the disorder are neurofibrillary tangles and amyloid plaques (Veerhuis, 2011).

Senile plaques, a pathologic hallmark of Alzheimer's disease, are associated with GFAP-positive activated astrocytes (Nagele *et al.,* 2004). It is reported that in various neuropathological states, the increased GFAP expression corresponds to the severity of astroglial activation (Axelsson *et al.,* 2011; Kashon *et al.,* 2004; Notturno *et al.,* 2009; Pelinka *et al.,* 2004; Simpson *et al.,* 2010; Toft-Hansen *et al.,* 2011).

Concerning astrocytes, recent findings suggest that they play a role in the clearance of the Aβ- peptide and thus in preventing plaque formation (Li *et al.,* 2011). Similarly, this peptide decreases glutamate uptake in cultured astrocytes, thus increasing oxidative stress and and activation of mitogen-activated protein kinase cascades (Agostinho *et al.,* 2010; Matos *et al.,* 2008). High levels of pro-inflammatory cytokines such as interleukin 1β, interleukin 6 and TNFα, mostly produced by reactive astrocytes, are detected in the brain of AD subjects, so the consequences of this phenomenon are unclear, also because pro-inflammatory cytokines have varied effects depending on the biological context (Veerhuis, 2011).

A previous study indicated that activated astrocytes were closely associated with amyloid plaques in the molecular layer of the cerebral cortex (Wisniewski & Wegiel, 1991). Astrocytes might be activated by human amyloid-β (Aβ) (DeWitt *et al.,* 1998), indicating a correlation between this protein and subsequent alterations in astrocyte function. Astrocytes also accumulate neuron-derived amyloid material resulting from local neurodegeneration. Once substantial accumulation of this debris occurs, the astrocytes themselves might undergo cell death, resulting in the formation of $GFAP^+$ amyloid plaques (Nagele *et al.,* 2004). *In vitro* analyses also indicate that treatment of astrocytes with Aβ results in an increase in calcium-wave signaling between these cells (Haughey & Mattson, 2003). In cells expressing the familial AD presenilin 1 (*PSEN1*) mutation, calcium oscillations in astrocytes were found to occur at lower ATP and glutamate concentrations than in wild-type astrocytes (Johnston *et al.,* 2006). These data support a model in which calcium signaling between astrocytes is altered by the disease process, which might, in ways that are not fully understood, contribute to dysfunction or death of neurons.

Either prooxidant agents or amyloid beta peptide did not cause deleterious effects in the astrocytes, but the combined treatment let to oxidative stress and apoptosis in vitro and inflammation and degenerative traits in vivo. Therefore, a reduced oxidative stress defense capacity in frail aged astrocytes may contribute to neuron death by failure of astrocyte support. To preserve astrocyte function and reduce oxidative stress in old age is a new goal against AD (Aliev *et al.,* 2009a; Aliev *et al.,* 2009b; Garcia-Matas *et al.,* 2010).

3.3 Parkinson´s disease

PD is the second most prevalent neurodegenerative disease, after AD. PD is estimated to affect about 1 million Americans, or about 1% of the population over 60 years of age. PD is caused by the disruption of dopaminergic neurotransmission in the basal ganglia. On pathological examination, the numbers of dopaminergic neurons in the substantia nigra are markedly reduced, and Lewy bodies (cytoplasmic inclusions) are present in the residual dopaminergic neurons (Nutt & Wooten, 2005). The focus has always been on the loss of these dopamanergic neurons and subsequent depletion of dopamine, but a role for non-neuronal cells in producing neuropathological or neuroprotective functions in PD is becoming increasingly recognized.

The studies that have been carried out to date appear to support a neuroprotective role for astrocytes in PD. From pathological examinations, an increase in the number of astrocytes as well as in GFAP expression is observed in PD, (Ciesielska *et al.,* 2009; Muramatsu *et al.,* 2003), as with other neurodegenerative disorders. The pathological evidence indirectly indicates that antioxidant pathways might contribute to this neuroprotective effect, because in control brains the density of glutathione-peroxidase-positive cells was higher in the vicinity of the dopaminergic cell groups known to be resistant to the pathological process of PD. The increase in glutathione-peroxidase-containing cells was inversely correlated with the severity of dopaminergic cell loss in the respective cell groups in patients with PD. The quantity of glutathione-peroxidase-containing cells, therefore, might be critical for a protective effect against oxidative stress (Damier *et al.,* 1993). Conversely, the presence of synuclein-positive astrocytes in pathological samples has been shown to correlate with nigral neuronal cell death (Wakabayashi *et al.,* 2000).

Nitric oxide production and glutathione depletion also appear as consistent features in human PD. The release of glutathione represents another pathway by which astrocytes might be neuroprotective in PD models. Glutathione production appears to be increased by exposure of astrocytes to nitric oxide, and the increase in glutathione release by astrocytes might increase its availability to neurons, thereby making them less susceptible to reactive nitrogen species. This pattern is consistent with the data in PD patients, in whom glutathione-containing cells are in regions with preserved dopaminergic neurons (Heales *et al.,* 2004).

Evidence regarding regulation of glutamate transporter expression and function in PD has been somewhat mixed, with downregulation of glutamate transporters being reported in some studies and upregulation being reported in others. The differences in these studies might be related to the methods by which the lesions were induced (Maragakis & Rothstein, 2004).

3.4 Amyotrophic Lateral Syndrome (ALS)

Amyotrophic Lateral Syndrome is an inexorably progressive motor neuron disease, in which both the upper motor neurons and the lower motor neurons degenerate leading to

muscle atrophy. Patients eventually experience respiratory failure, usually within three to five years from diagnosis. However, the onset of ALS may be subtle and early symptoms are frequently overlooked.

Common to familial and sporadic ALS is the loss of the astrocyte glutamate transporter EAAT2. Studies of the EAAT2 transporter in tissue from individuals with sporadic ALS showed a marked loss of up to 95% of astroglial EAAT2 protein expression and activity in affected areas of the CNS (Bristol & Rothstein, 1996). A clue to a possible mechanism for EAAT2 reduction or dysfunction was provided by the finding of aberrant *EAAT2* RNA species, which has been implicated in multiple neurodegenerative diseases. The production of truncated EAAT2 protein results in reduced function, and the retention of normal EAAT2 protein within the cytoplasm (Lin *et al.,* 1998). The significance of these aberrant *EAAT2* RNA species continues to be debated, however, as they have also been found in some normal controls (Flowers *et al.,* 2001; Meyer *et al.,* 1999).

In both human tissue and transgenic models of ALS, there is abundant evidence that astroglial abnormalities and physiological dysfunction precede clinical disease. These changes include reactive astrocytosis that can be seen many months before motor neuron degeneration (G85R) (Bruijn *et al.,* 1997), and loss of glutamate transport and GLT1 protein expression before the onset of clinical disease or overt motor neuron degeneration (Howland *et al.,* 2002). Similarly, increased astrocytes activation and expression of immune/inflammatory markers are hallmark of this pathology (Chiu *et al.,* 2008; Chiu *et al.,* 2009). Is the reduction in GLT1 protein in astrocytes significant? Guo and colleagues addressed this question by overexpressing the EAAT2 protein in astrocytes in the mSOD1 mouse model, and demonstrated an increase in motor neuron survival and a delay in disease onset; similar outcomes are seen with drugs that increase GLT1 expression (Guo *et al.,* 2003). This evidence indicates that EAAT2 expressed in astrocytes - and probably also glutamate- influences the timing of disease onset and motor neuron survival (Guo *et al.,* 2003). Other changes associated with ALS include increased expression of various proteins in astrocytes, including inducible nitric oxide synthase (iNOS), the copper chaperone CCS, and metallothioneins. Pathologically, early cytosolic proteinaceous aggregates have been found in spinal cord astrocytes from the entire mSOD1 mouse lines examined to date (Patel & Maragakis, 2002).

3.5 Multiple Sclerosis

Multiple Sclerosis is a chronic inflammatory demyelinating disease of the central nervous system in which glial cells play a prominent role. In murine experimental autoimmune encephalomyelitis (EAE), an established animal model of multiple sclerosis, astrocyte hypertrophy coincided with manifestation of axonal damage (Wang *et al.,* 2005). Astrocytes in multiple sclerosis plaques produce IL-6 (Okuda *et al.,* 1998), lack β-2 adrenergic receptors, and potentially serve as antigen-presenting cells (Zeinstra *et al.,* 2000b), thus facilitating T-cell invasion and activation. Repeated exposure of these astrocytes to inflammatory cytokines triggers unregulated inflammatory responses and increased noradrenalin levels, leading to focal areas of myelin and axonal damage (De Keyser *et al.,* 1999; Zeinstra *et al.,* 2000a).

Concerning the immune system, class II MHC expressing astrocytes have been shown to process and present antigens and activate both naïve and memory T cells (Nikcevich *et al.,* 1997; Soos *et al.,* 1998). In contrast, other investigators have shown that class II MHC expressing astrocytes are not capable of stimulating T-cell proliferation and instead induce

apoptosis or down-regulation of T cells (Matsumoto *et al.,* 1992; Weber *et al.,* 1994). Such a response may be beneficial for astrocyte suppression of CNS autoimmunity like in multiple sclerosis.

4. Conclusions

Astrocytes play a critical role in normal function of the mammalian nervous system. Astrocytes regulate K^+ buffering, glutamate clearance, brain antioxidant defense, close metabolic coupling with neurons, and modulation of neuronal excitability. In numerous pathological states, such as AD, PD, ALS and ME, astrocytes are involved in both exacerbation of damage and neuroprotective mechanisms. As discussed in this chapter, they support neurons in many ways, all of which are essential for repair and regeneration. Disturbances in astrocytic functions are implicated in neurodegenerative diseases pathogenesis, therefore, modulation of astrocyte functioning may prove to be an efficient therapeutic strategy in many chronic CNS disorders.

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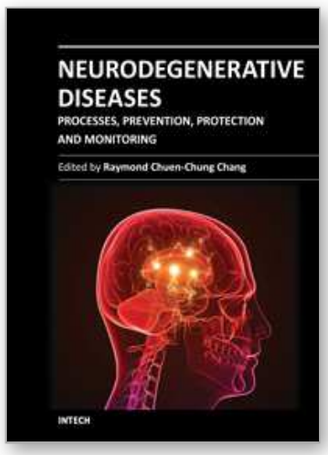

Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring

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Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring focuses on biological mechanisms, prevention, neuroprotection and even monitoring of disease progression. This book emphasizes the general biological processes of neurodegeneration in different neurodegenerative diseases. Although the primary etiology for different neurodegenerative diseases is different, there is a high level of similarity in the disease processes. The first three sections introduce how toxic proteins, intracellular calcium and oxidative stress affect different biological signaling pathways or molecular machineries to inform neurons to undergo degeneration. A section discusses how neighboring glial cells modulate or promote neurodegeneration. In the next section an evaluation is given of how hormonal and metabolic control modulate disease progression, which is followed by a section exploring some preventive methods using natural products and new pharmacological targets. We also explore how medical devices facilitate patient monitoring. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

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