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The role of astrocytes in the physiology and pathology of the central nervous system

Review

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Abstract. Astrocytes are the main class of neuroglia, serving a wide range of adaptive functions in the mammalian nervous system. They interact with neurons, providing structural, metabolic and trophic support for them. In pathological circumstances, astrocytes have the potential to induce neuronal dysfunction, but they can also play a neuroprotective role, releasing neuronal growth factors. Here we review recent findings regarding the role of astrocytes in the biology of the brain in physiological conditions, as well as their reaction following the onset of neurodegenerative disorders.

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Key words: astrocytes, neurons, microglia, neurodegenerative diseases, CNS

INTRODUCTION

Astrocytes are the most abundant cells in the central nervous system (CNS). Although they account for nearly half the cells in the brain, their function has been a long-standing neurobiological mystery. While astrocytes were for decades regarded as passive elements in the brain, affording structural and metabolic support to neurons, a new picture has been evolving in recent years. As a result of this evolution, astrocytes have been shown to be involved in the regulation of the brain microenvironment, in particular as regards neurotransmitter and ionic homeostasis, metabolic support of neurons, regulation of energy metabolism, synaptic transmission and neuronal excitability, synaptic generation, detoxification, free-radical scavenging, metal sequestration, development and maintenance of the blood-brain barrier, guidance of neuronal migration and immune function.

Astrocytes are dynamic cells that maintain homeostasis throughout the normal CNS. They express numerous receptors that enable them to respond to various neuroactive compounds, including neurotransmitters, neuropeptides, growth factors, cytokines, small molecules and toxins. These receptors enable astrocytes not only to participate in signal processing, but also to function as sentinels (Barbeito et al. 2004, Nedergaard et al. 2003).

Astrocytes secrete an enormous array of neurotrophic factors, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glia-derived neurotrophic factor (GDNF), ciliary neurotrophic factor (CNTF), glia-derived nexin (protease nexin-1), epidermal growth factor (EGF) and hepatocyte growth factor (HGF) (Nedergaard et al. 2003, Schmalenbach and Müller 1993). These factors are essential for the proliferation, survival and maturation of neuroblasts committed to a neuronal lineage (Villegas et al. 2003).

Astrocytes influence neuronal development and the activity of neurons at several levels, through direct cell-to-cell contacts and via humoral factors acting at short range (Környei et al. 2005). A variety of soluble and membrane-associated factors produced by astrocytes instruct neural stem cells to adopt a neuronal fate. In brief, astrocytes can control developmental neurogenesis (Nakayama et al. 2003). The current evidence indicates that astrocytes can also stimulate neurogenesis from subventricular zone progenitors (Villegas et al. 2003). In adulthood, the neurogenesis occurs in two specific brain regions: the subventricular zone and the hippocampal subgranular zone (Song et al. 2002a). The latter authors demonstrated that adult astrocytes from the hippocampus can promote neurogenesis, both by instructing stem cells to adopt the neuronal fate and by encouraging their proliferation (Song et al. 2002a,b). This effect is regionally specific, because astrocytes from the spinal cord do not have such a promoting potential as those of the hippocampus.

Astrocytes may also control neuronal life more directly, by regulating the production of synapses. They are capable of inducing and stabilizing CNS synapses, as well as modulating synaptic activity (Haydon 2000, Ullian et al. 2001, Villegas et al. 2003). It is now established that astrocytes are active participants in synaptic transmission. They express many neurotransmitter receptors which are stimulated during synaptic activity and initiate calcium signaling (Schipke and Kettenman 2004, Vesce et al. 1999, Villegas et al. 2003). In conditions of a high calcium concentration, increased release of neurotransmitters such as glutamate is observed, this being known as the main component in neuron-glia cross-talk during synaptic activity (Nedergaard et al. 2003, Villegas et al. 2003). Although glutamate and ATP are the most well known “gliotransmitters” it is now obvious that D-serine can be added to the list of neuromodulators (Wolosker et al. 2002). Recent literature has unveiled multiple roles for D-serine in CUN. It promotes synaptogenesis and synaptic plasticity (Martineau et al. 2006). There is no consensus about how astrocytes regulate D-serine levels at synapses. Activation of glutamate receptors causes the release not only glutamate but also D-serine (Mothet et al. 2005). It suggests that glutamate release triggers glial D-serine efflux which in turn modulates the NMDA receptors at postsynaptic sites. D-serine is an endogenous ligand for NMDA receptors and it has the ability to control NMDA-receptor-dependent neurotransmission. However, because D-serine regulates NMDA receptor’s activity, their excessive activation in the presence of glutamate may also cause neuronal death. In such a pathological condition D-serine compromises the survival of neurons by exacerbating the effect of glutamate. Astrocytes as dynamic partners of neurons at synapses control synaptic transmission by sensing the level of synaptic activity and in turn influencing synaptic activity by regulating release of neuromodulators. Such neuron-to-astrocyte signaling has also been described

for several other neurotransmitters, such as noradrenaline, acetylocholine and GABA (Duffy and MacVicar 1995, Kang et al. 1998, Shelton and McCarthy 2000)

Astrocytes also have a dialogue with neurons *via* gap-junction channels joint by connexin proteins. Gap junctions allow for direct electrical and biochemical communication and support astrocytic key functions, such as shuttle of metabolic substrates and spatial K^+ buffering (Bezzi and Volterra 2001, Rouach et al. 2002, Villegas et al. 2003). Finally, astrocytes are not only of great importance in synaptic formation and function, but are also involved in synaptic elimination *via* the reduction of synaptic contacts. This denotes a major role in structural plasticity.

Several cytokines are expressed constitutively in the normal CNS, though the majority of data indicate that they are present at very low levels in physiological conditions (Kielan and Drew 2005). Astrocytes are capable of synthesizing certain cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and transforming growth factor-β (TGF-β). An increase in the array of cytokines, enzymes, extracellular matrix molecules and heat-shock proteins has been described in reactive astrocytes (Norenberg 2005).

Astrocytes commonly undergo a dramatic transformation referred to as reactive astrocytosis or astrogliosis, which is the most prominent cellular response to diverse forms of CNS injury. Reactive astrogliosis is associated with cellular hypertrophy, astrocyte proliferation, process extension and interdigitation (Ridet et al. 1997). Increased production of the intermediate filaments glial fibrillary acidic protein (GFAP), vimentin and nestin (Liberto et al. 2004) is observed. However, enhanced expression of most of these molecules is not limited to reactive astrocytes. The astrocytic reaction appears to be miscellaneous, modulated by different changes in microenvironmental conditions, the combinations of cytokines, growth factors, adhesion molecules and other damage signals originating from injured neurons, proliferating microglia, and endothelial cells, or from extravasted blood or serum (Ridet et al. 1997). As astrocytes become activated, the microglial reaction can be regarded as necessary for the typical inflammatory response of brain tissue to a variety of insults. There is a close relationship between astrocytes and microglia, which are known as immune effector cells of the central nervous system. Microglia produce inflammatory molecules such as interleukin-1β (IL-1β), interleukin-6 (IL-6) and transforming growth factor-β (TGF-β). However, the relationship between astrocytes and microglia is not as yet well understood. Nevertheless, it is the balance between microglia and astrocytes that maintains neuronal homeostasis, such that changes in the constellation of these cells may lead to a number of neurological dysfunctions. Both cell types are involved in the balance of destructive or protective actions that characterises the pathogenesis of neurological disorders (Vernadakis and Lambropoulos 2000).

ASTROCYTES AND CEREBRAL ISCHEMIA

The occlusion of a major cerebral blood vessel results in tissue damage that evolves and spreads over time, initially encompassing the severely ischemic focus. The rapid reduction in blood flow can be detrimental to neurons as well as astrocytes, leading to pannecrosis in the ischemic core. Recent findings demonstrate that in both cells, intermediatory metabolism is similarly impaired after 30 min of focal ischemia (Hagberg et al. 2001). Protective astrocytic function such as glutamate uptake, K^+ buffering and the elimination of free radicals will be compromised under these conditions.

The astrocyte swelling often observed following focal cerebral ischemia leads to an increase in intracerebral pressure, a reduction of vascular perfusion, and exacerbation of the ischemic event (Ayata and Ropper 2002). Brain edema is a common cause of delayed death after a stroke in humans. Astrocyte swelling may also induce further glutamate release, whereas the reduction in extracellular space alters the ion concentrations – which can themselves affect both neuronal and astroglial excitability further. Reduced uptake and increased release of glutamate by surrounding astrocytes can contribute to excitotoxic mechanisms, such as the activation of glutamate receptors and subsequent influx of calcium ions into neurons. Increased intracellular Ca^{2+} concentration enhanced by its release from intracellular stores results in uncontrolled activation of many enzymes, i.e., neuronal protein kinases, phospholipases, proteases and NO synthase involved in the initiation of signals that produce delayed cell death after ischemia (Anderson et al. 2003).

As astrocyte gap junctions remain open during ischemia, this may contribute to induced cell death in

the prenumbral region (Cotrina et al. 1998). A number of hypotheses have been advanced to account for this phenomenon. Firstly, proapoptotic substances can diffuse from dying cells in the ischemic core to healthy cells, causing their delayed damage (Lin et al. 1998). It is also possible that calcium waves spreading *via* gap junctions to the prenumbral region can be involved in the excitotoxic death mechanism (Budd and Lipton 1998).

Astrocytes also have a beneficial role in promoting the survival of different brain cell types in ischemic lesions. The part they play in the anti-oxidant defense of the brain is considered crucial, since they contain the highest concentrations of antioxidants, as well as provide the neurons with substrate for important antioxidative pathways that lead to the glutathione reduction (Chen et al. 2001, Dringen et al. 2002). Furthermore, astrocyte-released growth factors and other molecules are able to prevent cell death and may facilitate activation of neurogenesis following injury. Moreover, they are the major component of the so called "glial scar" probably representing an attempt by the CNS to isolate viable tissue from a damaged region, with a view to protecting surrounding cells from the harmful substances released within the infarct core. Although this process of separating the area of damage may be beneficial, its long-term consequence may be the establishment of a barrier inimical to regeneration of the CNS.

The astrocytic response to stroke may thus be considered extremely complex and incompletely understood. On the one hand, astrocytes may contribute to damage by sending apoptotic messengers or other deleterious molecules to healthy regions *via* the gap junction channels. They may also inhibit regeneration by forming the glial scar. On the other hand, however, astrocytes protect neurons against high levels of glutamate and the depression-spreading depolarizing K^+ concentration present in the extracellular space. Furthermore, the astrocytic production of potentially neuroprotective growth factors may affect cell proliferation and neurogenesis positively.

The exposure of glial cells to a pathological (e.g., ischemic) or toxic insult triggers a reactive response through which pro-inflammatory or anti-inflammatory cytokines capable of affecting neuronal function are released. The general assumption is that pro-inflammatory cytokines (i.e., TNF-α, IL-β) exacerbate and sustain neurodegeneration, whereas their anti-inflammatory counterparts (i.e., IL-10, TGF- β) promote neuronal survival. The observation that glial cells can be induced to produce cytokines capable of modulating neuronal functions has revolutionized the concept of neurotoxicity, which was always believed to reflect direct interaction of toxicants exerting an activating influence upon neurons' responses to injury. Thus, glia can either exacerbate neuronal damage or favor recovery, in relation to the types of cytokines produced (Fig.1).

ASTROCYTES AND BRAIN INFLAMMATION

Astrocytes and microglia are the brain representatives of the general immune system, and can act under pathological conditions as immune competent cells. Upon activation, the reactive glial cells gain a number of potentially neurotoxic potencies, e.g., *via* the release of inflammation-promoting mediators and oxidative radicals. As long as these factors remain under strict control, reactive glial cells can be seen to play an undoubtedly beneficial role in defense and repair. However, an escalating pathological glial activation which involves both microglia and astrocytes may contribute to secondary nerve-cell damage.

Astrocytes are being shown to have important functions when it comes to the initiation and regulation of CNS immune responses mediated *via* the release of pro-inflammatory cytokines, i.e., TNF-α, IL-1β, IL-6 and TGF-β1 (Dong and Benveniste 2001). Alongside the beneficial effect glia have in initiating protective immune responses in the CNS, is their implicated role in contributing to tissue damage once chronically and/or pathologically activated.

Activated astrocytes are a major source of TNF-α in an inflamed CNS. The implications of TNF-α expression in various neuro-inflammatory diseases may be complex and influenced by the nature of the CNS insult, the timing of its expression during disease or the local concentration of TNF-α achieved within the CNS microenvironment. The numerous effects of TNF-α within CNS tissue include modulation of BBB integrity and activation of resident glia or infiltrating peripheral immune cells. In addition, *in vitro* studies have revealed the neurotoxic impact of TNF-α produced by activated astrocytes co-cultured with neurons, this most likely contributing to the significant neuronal loss associated with many CNS inflammatory diseases (Kielan and Drew 2005).

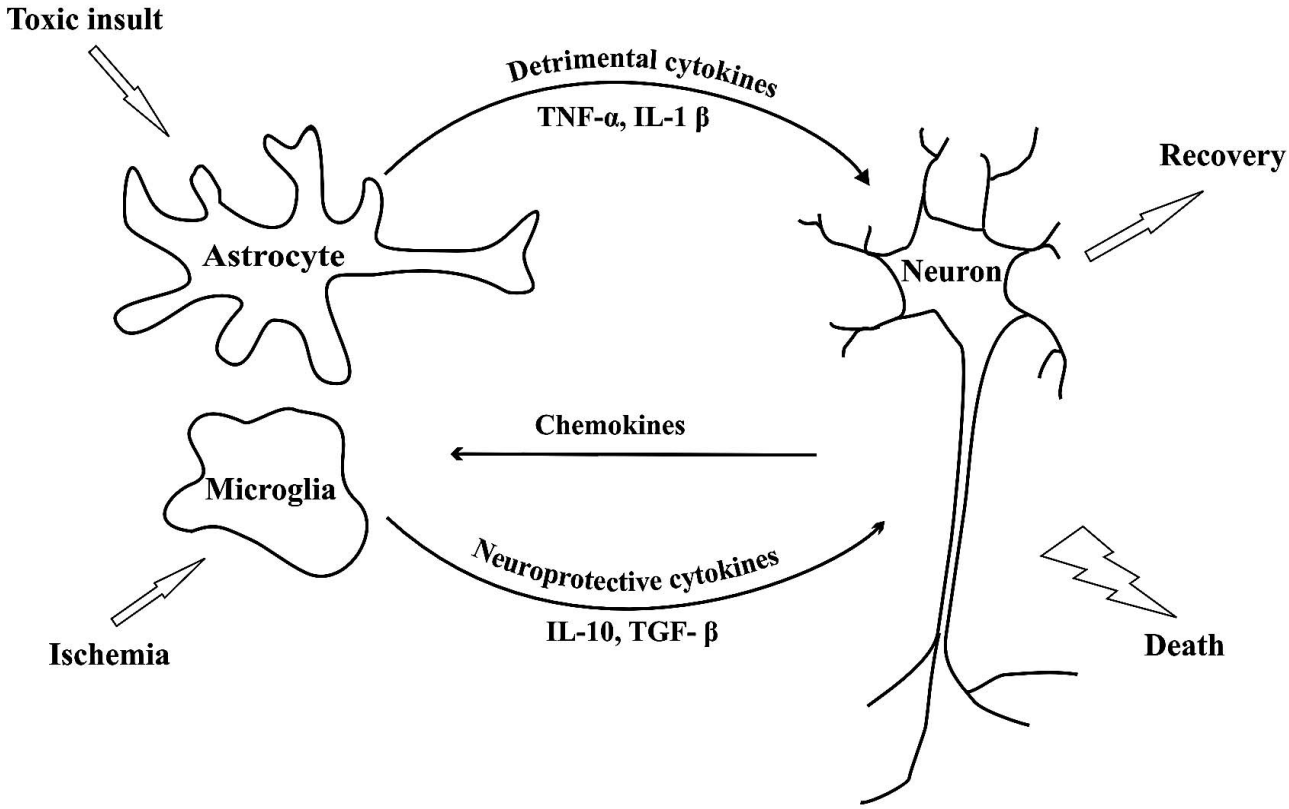

Fig. 1. The cytokine cycle as a glial-neuronal interaction in ischemia or toxic insult (according to Viviani and Marinovich 2005, modified). Exposure of glial cells to pathological conditions leads to the release a wide range of cytokines that have impact on neuronal survival. Pro-inflammatory cytokines, i.e., TNFα, IL-1β exert detrimental effect while anti-inflammatory cytokines, i.e., IL-10, TGF-β have neuroprotective task. In turn factors derived from neurons attune glial cell response.

Like TNF-α, IL-1β has a similar array of effects during CNS inflammation, resulting in the production of additional cytokines, such as IL-6. IL-1β is produced by both activated astrocytes and microglia, and has been shown to have cytotoxic effects on different cell types in the CNS, including oligodendrocytes and neurons. This finding suggests that IL-1β may contribute to neurodegeneration in the context of CNS inflammatory diseases (John et al. 2003).

Astrocytes serve as the main source of IL-6 and TGF-β1 in the inflamed CNS, the former being a multifunctional cytokine whose diverse roles include the regulation of acute-phase reactions and immune responses and the promotion of astrocyte proliferation and neuronal survival – suggesting a dual role in dictating beneficial vs. detrimental responses in neuroinflammation (Gruol and Nelson 1997). TGF-β is in turn a complex cytokine that possesses anti-inflammatory properties. Most of the cells producing TGF-β in the adult CNS are astrocytes (Unsicker and Strelau 2000), and the cytokine may help down-regulate CNS neuro-inflammatory responses.

In general, inflammation is detrimental to neurogenesis in the adult brain. Brain inflammation causes inhibition of both the continuous basal formation of new neurons in the intact brain and the augmented neurogenesis that brain insult may stimulate. Glia-activation specifically compromises the survival of new neurons, the deleterious effect of activated microglia on newly-formed cells most likely being mediated through the action of such cytokines as IL-1β, IL-6 and TNF-α, as well as through increased production of reactive oxygen species (Ekdahl et al. 2003). However, depending on its spatio-temporal occurrence, glia activation following brain damage may probably be beneficial, in that it promotes other aspects of regeneration, as through the release of neurotrophic molecules.

It is conceivable that the relative importance of the harmful and helpful actions of glia under various cir-

cumstances will determine the behavioral consequences of brain inflammation. CNS inflammation may plausibly be of importance in the pathogenesis and progression of such chronic neurodegenerative disorders as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS).

ASTROCYTES IN ALZHEIMER'S DISEASE

The progressive, age-related neurodegenerative disorder known as Alzheimer's disease (AD) is the commonest form of dementia in later life, manifested in progressive memory impairment problem solving and language difficulties (aphasia, anomia) planning and abstract thought deficits in motor spatial skills (apraxia) and visual spatial skills (agnosia) and cortical dementia. Histopathological features include the presence of senile plaques (SPs) or neurofibrillary plaques (NFTs) and neurofibrillary tangles, the preferential loss of cholinergic and cholinoceptive neurons (especially in areas of the frontal cerebral cortex and hippocampus) and the presence of activated macrophages and reactive astrocytes (Minagar et al. 2002, Nagele et al. 2003). SPs are deposits of extracellular ß-amyloid protein (Aß) derived from amyloid β (1-42) (Aβ42), a peptide fragment of 42 amino-acid residues derived from selective proteolytic cleavage of amyloid precursor proteins (APP) through the sequential actions of β- and γ-secretases. In turn, NFTs are intraneuronal structures composed of tau protein (Tuppo and Arias 2005). β-amyloid is a potent and direct neurotoxic agent and it induces a cascade of cellular mechanisms including activation of astrocytes, which leads to neuronal damage (Holroyd and Shepherd 2001).

Several lines of evidence suggest that inflammation contributes to the neuropathology associated with AD. Interaction of microglia and astrocytes is another significant aspect of AD pathogenesis. Through the production of neurotoxic molecules, astrocytes and microglia are involved in the disease's inflammatory process. The microglial cells are activated *via* the cellular response to such pathological factors as the Aβ and neuritic plaques (Kalaria 1999). In response, they produce TNF-α and other cytokines, and consequently promote the secretion of reactive oxygen species, and hence further damage neurons *via* free-radical oxidative damage. Activated microglia are capable of producing the pro-inflammatory cytokines IL-1β, IL-6 and TNF-α (Schubert et al. 2001), as well as such chemokines as interleukin-8 (IL-8), macrophage inflammatory protein-1α (MIP-1α) and monocyte chemo-attractant protein-1 (Rogers and Lue 2001). The microglia-released cytokines and reactive oxygen species can activate surrounding astrocytes (Fig. 2).

The role of astrocytes in the inflammatory process associated with AD is more difficult to ascertain (Tuppo and Arias 2005). Reactive astrocytes are seen to surround SPs, while astrocytes cluster where Aβ is deposited. Electron microscopy of AD brain tissue reveals deposition of Aβ in astrocyte processes (Kurt et al. 1999). Activated astrocytes are seemingly capable of internalizing (*via* phagocytosis?) the debris that is released by dying and/or from dead neurons, which comprises neuron-specific proteins as well as Aβ. To test this idea, Nagele and coauthors (2003) cut histological sections through the enthorinal cortex of AD brains and immunostained them with antibodies against the cholinergic neuron-specific protein ChAT and cholinoceptive-specific α7nAChR protein. Double immunolabeling with GFAP- and ChAT-specific antibodies revealed the presence of abundant intracellular ChAT in GFAP-positive activated astrocytes. The same was true of α7nAChR protein. By contrast, both ChAT- and α7nAChR-specific immunoreactivities were barely detectable in astrocytes of control brains (Nagele et al. 2003).

Work on the three-dimensional reconstruction of SPs in various stages of their formation suggests that, while microglial cells tend to be involved in plaque-formation, astrocytes are the major factor in plaque-degradation (Wegiel et al. 2000). In addition, astrocytes activated by Aβ produce the cytokines IL-1β, TNF-α and TGF-β, chemokines, complement proteins, thromboxanes, coagulation factors, proteases, protease inhibitors and reactive oxygen species which may be the direct cause of neuronal damage (Johnstone et al. 1999). Chemokines released by astrocytes attract microglia, which further express pro-inflammatory products, thereby contributing to yet further neuronal damage (Tuppo and Arias 2005).

Astrocytes were found to over-express S100β in neuritic plaques (Tuppo and Arias 2005). Astrocyte activation induced by IL-1β or IL-6 results in markedly enhanced S100 β gene expression (Mrak and Griffin

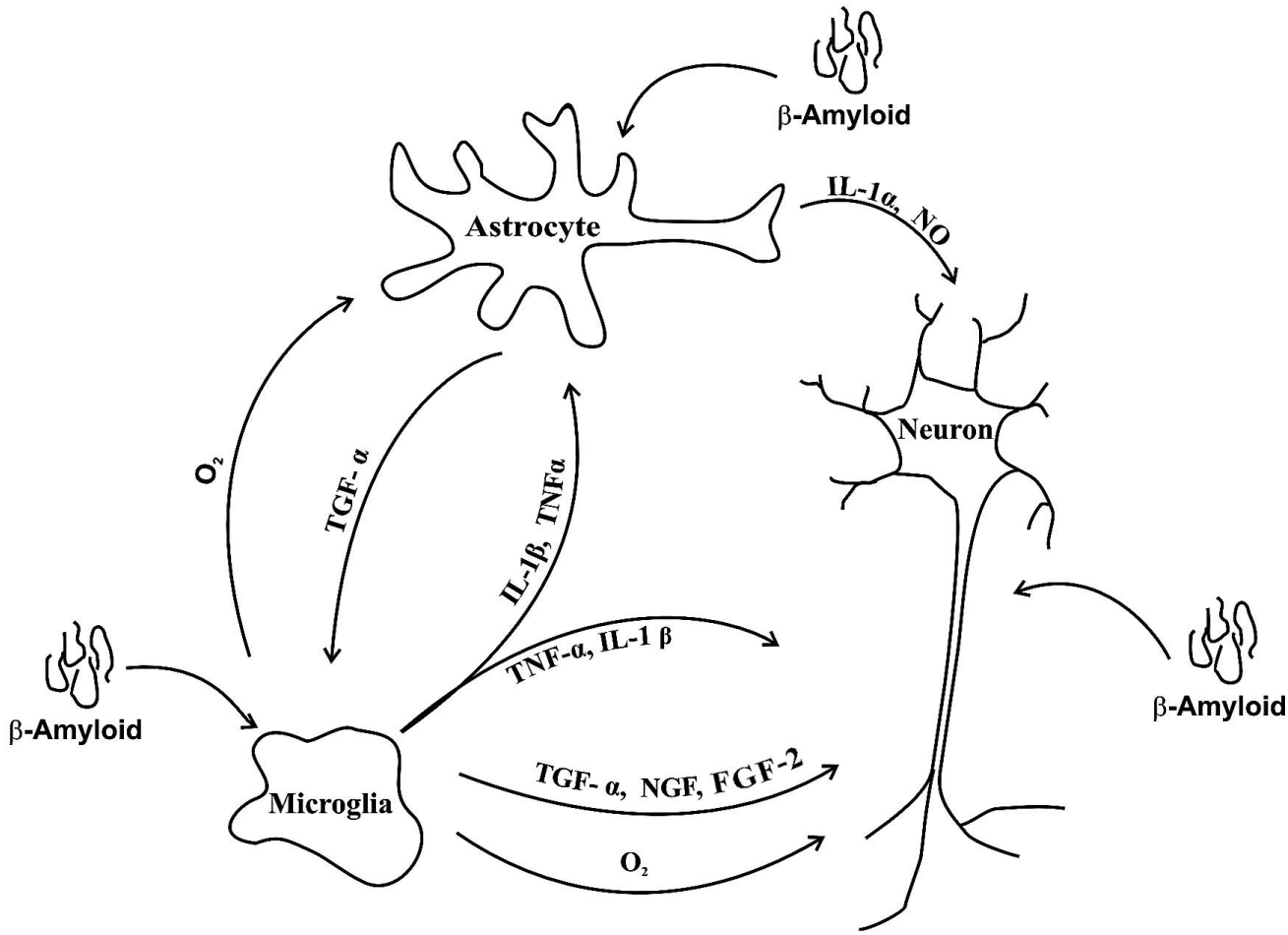

Fig. 2. Scheme of neurodegenerative cascade in AD (according to Minagar et al. 2002, modified). β-Amyloid is direct neurotoxic agent and induces activation of astrocytes and microglia which leads to neuronal damage. This is associated with production of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), neurotrophic factors (NGF, FGF-2) and reactive oxygen species.

2001). Compared to control ones, AD brains are also found to have high levels of NOS-positive astrocytes (Simic et al. 2000), suggesting neuronal damage through increased production of nitric oxide (NO) in AD brain.

Astrocytes may exert protective effects in the neuropathogenesis of AD, by inhibiting activated microglia. For example, the TGF-β they produce may help suppress iNOS activity in microglia (Vincent et al. 1997). In addition, *in vitro* cell-culture studies demonstrate a role for astroglial cells or astrocyte-conditioned medium from non-differentiated and highly proliferative cultures in the marked suppression of both phagocytosis of senile plaque cores by activated microglia and NO production. The inflammatory reaction is promoted in this way (De Witt et al.1998).

ASTROCYTES IN PARKINSON'S DISEASE (PD)

Idiopathic Parkinson's disease is a movement disorder, affecting about 1% of the over-60s. Its etiology is characterized by accelerated loss of dopaminergic neurons in the pars compacta of the substantia nigra (Schipper 1996). The three main motor features of Parkinson's disease are rest tremor, rigidity and bradykinesia (difficulties with fine motor tasks) (Samii et al. 2004). Various non-motor symptoms are also seen, including autonomic dysfunction, cognitive and psychiatric changes, sensory symptoms and sleep disturbances. There is mounting evidence that the excessive production of neurotoxic free-radicals may play an important role in this disorder's pathogenesis (Schipper 1996). In PD, the presence of reactive astrocytes and microglia is associated with an inflammato-

ry response, and the production of a wide variety of inflammatory molecules, including complement (Singhrao et al. 1999).

Under normal conditions, striatal neurons are protected by an efficient glutamate transport system in astrocytes, mediated by the glial glutamate transporter GLT-1. However, the transporter function is markedly impaired under the conditions of oxidative stress present in PD. Experimental *in vivo* studies have established that the striatal neuron damage is due to increased excitatory activity. Treatment with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) mimics the progressive nature of PD, with the functionality of the glutamate transporter system changed completely. Moreover, MPTP treatment is associated with an increased presence of GFAP-immunoreactive astrocytes in the striatum. These display a reactive morphology with thickened processes, the cells in question often being located close to the ventricle and along the corpus callosum. The GFAP-immunopositive cells are typically grouped into small clumps following the course of blood vessels. Each astrocyte has a tightly-configured set of fibrous processes that are initially thick, but rapidly become fine and wispy at the distal end (Dervan et al. 2004).

There is evidence to suggest a role for neuroinflammation in the degeneration of dopaminergic neurons in PD patients. A variety of cytokines are expressed at higher levels in the substantia nigra and/or striatum of patients with PD, as compared with control subjects. These include the TNF-α, IL-1ß, IL-6 and TGFβ known to be produced by glia (Nagatsu et al. 2000), the first two being directly toxic to neurons. On the other hand, TGFß is an inflammatory cytokine capable of suppressing glial activation and hence aiding in the resolution of inflammation associated with PD.

ASTROCYTES IN HUNTINGTON'S DISEASE (HD)

Huntington's disease is a genetic neurodegenerative disorder caused by an expanded CAG repeat in a gene coding for the protein huntingtin. There is selective death of striatal and cortical neurons and development of gliosis mainly involving microglia and astrocytes in the striatum (Petersen et al. 1999). Abnormal huntingtin in affected neurons is thought to lead to activation of excitatory amino-acid receptors, increased intracellular calcium concentrations and the generation of toxic free-radicals that can initiate the widespread scenario described above. The early stages of HD involve selective loss of neurons from the caudate nucleus, though without any significant gliosis. In disease progress, neuronal loss from the caudate increases considerably, with a concomitant induction of reactive astro- and microgliosis, particularly in the caudate gray matter. The number of GFAP-positive cells displaying the typical morphology of reactive hypertrophied astrocytes is significantly elevated in HD in the gray matter of the caudate. Reactive microglia in HD caudate express the increased levels of complement proteins and markers of inflammation. The formation of the membrane attack complex (MAC) is particularly significant as it demonstrates activation of the complement cascade inducing cytotoxicity and cytolysis. While no complement activation products have been observed in the cortical areas of HD brains, they are abundant in the HD caudate, being correlated with anaphylatoxin receptors. Aggregates of huntingtin provide for complement activation, suggesting that activation of local inflammation and cell gliosis are key factors in the neuropathogenesis of Huntington's disease. Singhrao demonstrated the anaphylatoxin receptor C5aR and C3aR mRNAs are expressed abundantly in HD caudate as well as the C4 mRNA is 8 fold higher in HD striatum compared to the level in normal control brain tissue. The C5aR and C3aR expression may play a role in the recruitment and activation of glial cells to express increased level of proinflammatory cytokines and complement proteins. The mechanism responsible for the selective cell death remains unclear. An attractive hypothesis emerged from work on transgenic mouse for exon 1 of the huntingtin gene (HD mouse) and cell culture models of hyperexpression of huntingtin with long polyglutamine (CAG) repeats. The huntingtin aggregates are ubiquitinated and form intra-nuclear inclusions, which are toxic and can induce programmed death of neurons (Singhrao et al. 1999). These inclusions contain NH_2 terminal fragments of the ubiquitinated mutant huntingtin. They have the spherical shape and appear prior to symptomes. In this model of HD there are also some changes in nuclear membrane such as indentations and increased pore density (Petersen et al. 1999). Curiously, neuronal loss and reactive gliosis in the striatum which are characteristic of human HD were not so evident in HD transgenic model. This observation strongly suggests the potential role of

other cytotoxic and inflammatory molecules which can amplify the primary neurotoxicity of human huntingtin (Singhrao et al. 1999).

ASTROCYTES IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Amyotrophic lateral sclerosis is a devastating neurodegenerative disease, characterized by selective degeneration of selective populations of motor neurons from the cortex, brainstem and spinal cord, leading to progressive paralysis and muscle atrophy (Shyam et al. 2003). Oxidative damage and disruption of extracellular glutamate homeostasis are involved in this selective loss of motor neurons (Barbeito et al. 2004).

There is a strong glial (isomorphic gliosis) response of cells surrounding motor neurons in ALS patients (Strong 2003). The reactive astrocytes involved manifest increased immunoreactivity for GFAP and S100 β, and express inflammatory markers such as COX-2, iNOS and neuronal NOS. In animal models of ALS/SOD1, astrocytes have demonstrated the major morphological and functional changes; aggregates formed by oxidatively-modified phosphorylated neurofilaments (NF), as well as reduced expression of glial glutamate transporter GLT-1 on account of RNA misplicing (Barbeito et al. 2004). Functional abnormalities and the selective reduction in amounts of GLT-1 may explain the significantly reduced capacity to transport glutamate in ALS (Barbeito et al. 2004), and the consequent increase in extracellular glutamate levels that promotes excitotoxicity.

As ALS is an age-dependent neurodegenerative disease, the astrocytic reactive changes resemble those in the aging brain (with an increased number of reactive astrocytes and up-regulation of GFAP and S100 β). Moreover, microglia proliferate along with astrocytes, and become activated in these regions. The astrocyte activity correlates with expression of such inflammatory mediators as cytokines, chemokines, growth factors and adhesion molecules, as well as with increased production of reactive oxygen and nitrogen species and defective glutamate homeostasis capable of leading to motor neuron degeneration (Barbeito et al. 2004).

The cross-talk between astrocytes and microglia is the basis for the pathogenesis of ALS. Microglial release of IL-1β results in astrocytic activation, an induced up-regulated expression of COX-2 enzyme and further production of pro-inflammatory cytokines and prostaglandin E2 (PE2) to stimulate glutamate release from astrocytes (Strong 2003). Activated astrocytes can produce IL-6, which promotes the survival (prevents the degeneration) of neurons, as well as self-proliferation and activation (Barbeito et al. 2004).

Surprisingly, a potential apoptotic candidate released by astrocytes is NGF: normally a key factor in the differentiation and survival of neurons during development and in the neural plasticity of the mature nervous system, that signals through the high-affinity TRkA receptor, becomes a death molecule if signals through $p75^{NTR}$ receptors exclusively. Motor neurons in ALS patients and G93A mutant mice are unresponsive to NGF because of a lack of the Trk A and $p75^{NTR}$ receptors. In the ventral horn of symptomatic G93A mice, NGF immunoreactivity was localized mainly in reactive astrocytes, and correlated with $p75^{NTR}$ expression in neighboring motor neurons (Pehar et al. 2004).

Oxidative stress caused by increased production of nitric oxide and peroxynitrite forms from damaged motor neurons may constitute a potential mechanism for astrocyte activation in ALS. The oxidative stress and peroxynitrite in reactive astrocytes can induce long-term effects in specific proteins, such as connexins, glutamate transporters and enzymes that may dramatically affect the interactions between astrocytes and neurons. Reactive oxygen species induce oxidation and disruption of glutamate uptake in neighboring astrocytes. In brief, this inhibits astrocytic glutamate transporters, causing increased neurotoxic influence on motor neurons through potentiating neuronal excitability and excitatory neurotransmission (Barbeito et al. 2004). The death of the motor neurons does not occur in isolation. It is clearly just the final event of an intricate triad of motor neuron, microglia and astrocytic interactions in which motor neuron damage may be a self-propagating process in which the initial neuronal injury induces a microenvironmental response by signaling to the adjacent microglia, which in turn upon activation, propagate the disease to neighbouring otherwise innocent motor neurons through the release of a number of soluble factors, including TNF-α, pro-inflammatory cytokines, NO and glutamate. The excitotoxic effect of high concentration of glutamate fails to be taken up by astrocytes deficient in EAAT2 transporters, resulting in the exposure of the motor neurons to chronic glutamate toxicity (Fig. 3).

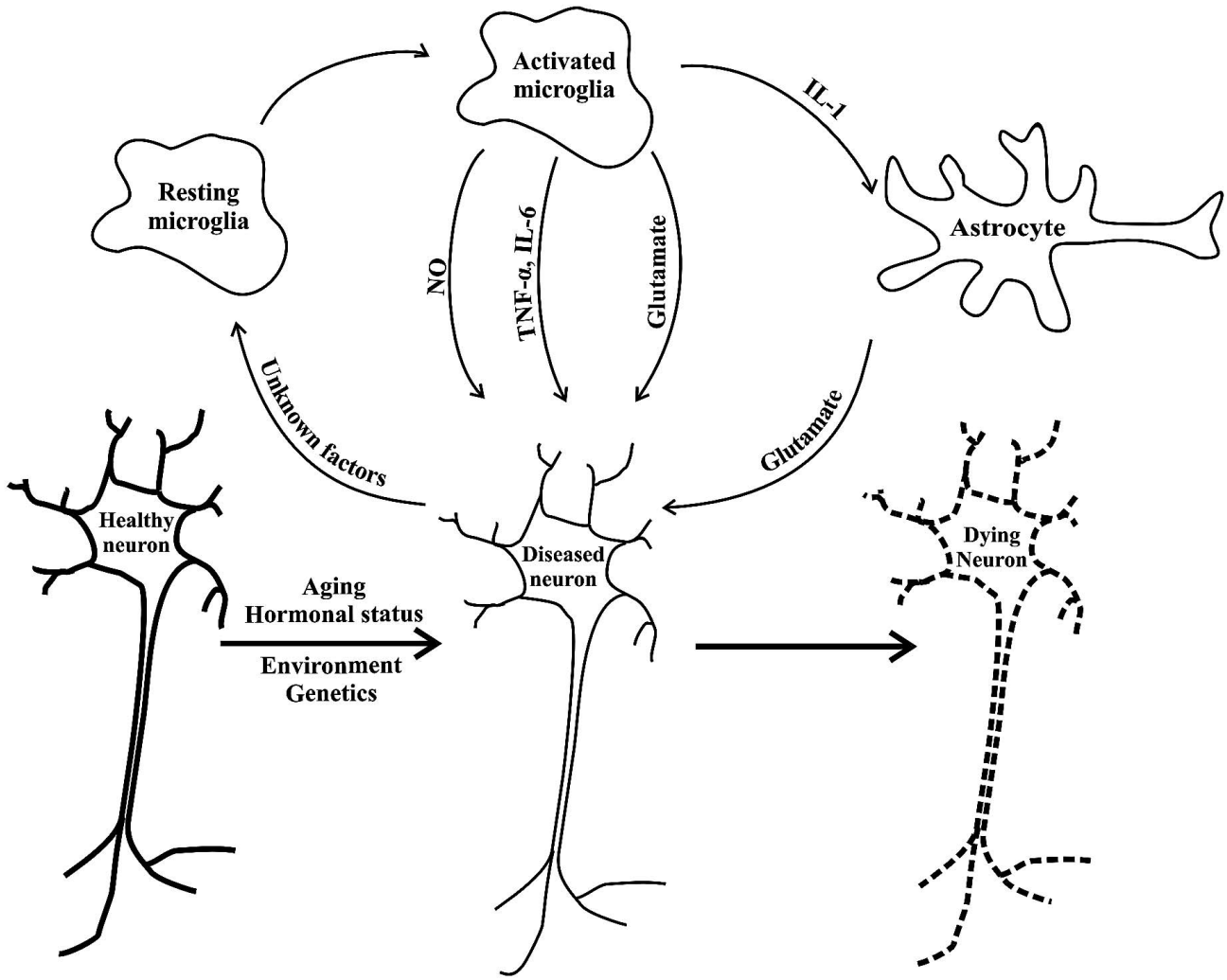

Fig. 3. Interaction of glia and neurons in ALS pathogenesis (according to Strong 2003, modified). Diverse factors, i.e., environment, genetics, aging, hormonal status contribute to motor neuron injury. Injuried neurons signal the activation of microglia which release TNF-α, IL-1β, IL-6, NO and glutamate mediating further neuronal injury. High concentration of glutamate produced by activated microglia and astrocytes sustain chronic glutamate toxicity to the motor neurons.

ASTROCYTES IN MULTIPLE SCLEROSIS (MS)

Multiple sclerosis (MS) is the most common disabling neurological disease among young adults. MS is associated with immunological aberrations involving several cell groups (astrocytes, activated microglia and oligodendrocytes). Clinically, MS manifests itself in fatigue and disturbed function in the sensory, motor, bladder and bowel, cerebellar, optic-nerve and cognitive realms. MS is an inflammatory disease of CNS white matter. Inflammatory cells present – mainly activated lymphocytes and macrophages – penetrate the white matter surrounding the blood vessels, destroying myelin, though usually (but not always) sparing axons.

Activated microglia and astrocytes play a major role in the inflammatory and immune responses in MS demyelination (Minagar et al. 2002). The balance and interactions between astrocytes and activated microglia play a significant role in MS activity (Xiao and Link 1999). Activated microglial cells are responsible for presenting the antigens (APC cells) in inflammatory MS neuronal lesions. They also synthesize and release proteases, TNF-α and NO. These last molecules may damage oligodendrocyte myelin units, and then bring about demyelization (Xiao and Link 1999). Moreover, astrocytes and microglia engage in a dialogue *via* cytokines (Minagar et al. 2002). The IL-1, IL-6 and TNF-α generated by activated microglia

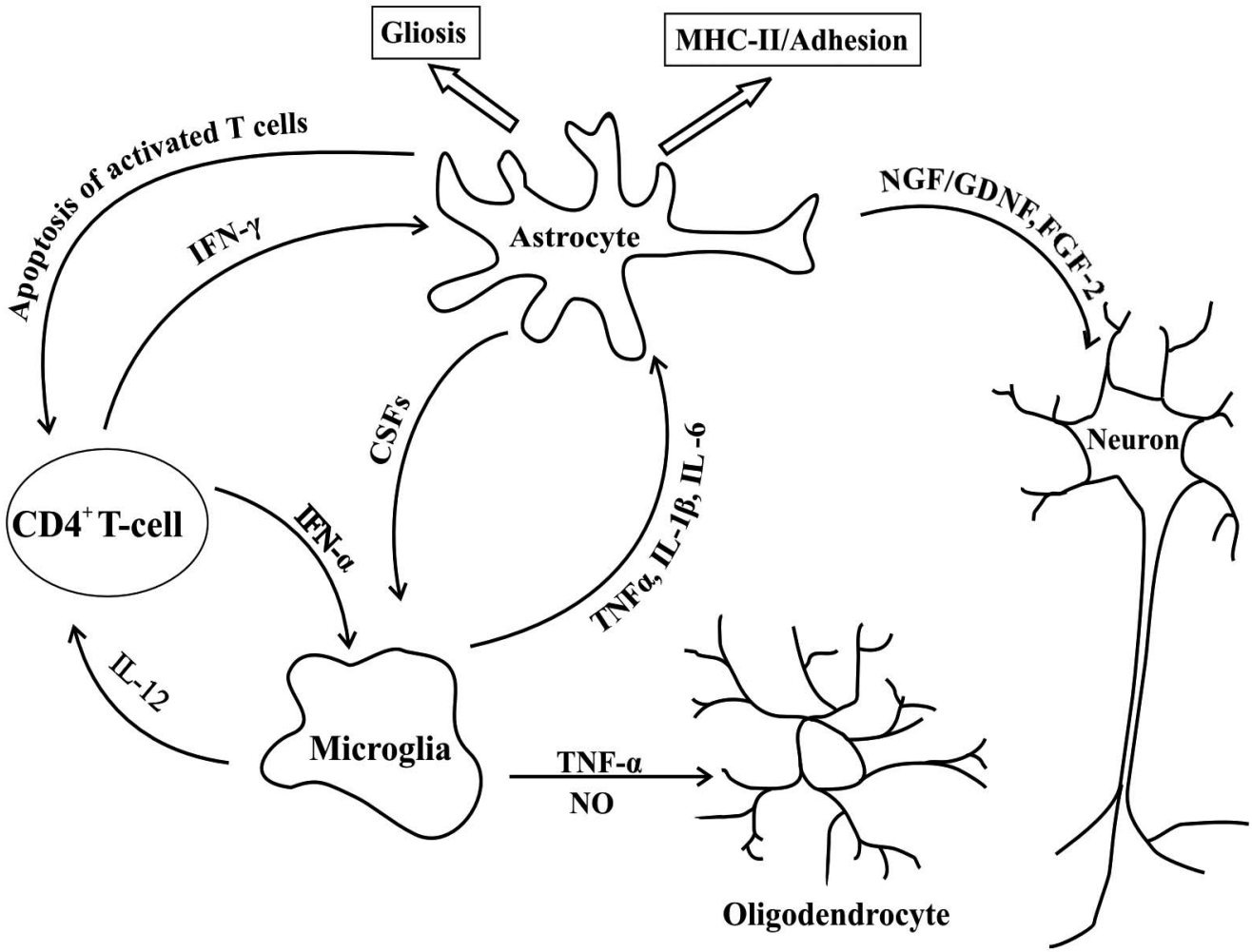

Fig. 4. Interactions between activated astrocytes, microglia, T cells and oligodendrocytes in MS (according to Minagar et al. 2002, modified). Activated microglia present foreign antigens to $CD4^+$ T cells. Activated T cells secrete IFN-γ which further activates microglia to produce IL-1β, IL-6 and TNF-α stimulating astrogliosis. Astrocytes produce CSF-s that exert microglia growth. Activated microglia release TNF-α and NO that are crucial for damage oligodendrocytes and myelin.

induce astrogliosis, building a physical barrier to further remyelination (Compston and Coles 2002). Astrocytes also produce colony-stimulating factors (CSFs) that are crucial to the sustained growth of microglia (Minagar et al. 2002) (Fig. 4).

It is now also established that the IL-12, which is crucial in the development of an immune response, produced by microglia plays a central role in MS pathogenesis. Co-culture studies with astrocytes or exposure to astrocyte-conditioned media show that astrocytes regulate the production of IL-12 by microglia (Xiao and Link 1999). Moreover, such anti-inflammatory cytokines as IL-4, IL-10 and transforming growth factor β (TGF-β) seem to be associated with down-regulated inflammation and hence remission. Recent research shows that IL-12 and IL-10 are possible markers of disease status in MS (Miller et al. 2004).

Of major importance is the fact that astrocytes express major histocompatibility (MHC) class-II molecules in the active lesions of MS, and may also play an important role in the presentation of antigen to myelin-specific T-cells. Astrocytes do not normally express MHC class-II molecules constitutively, because of a number of regulatory influences such as norepinephrine-induced cAMP elevation through the activation of the β_2 adrenergic receptor (Zeinstra et al. 2003). However, Zeinstra and others (2003) report that astro-

cytes in the cerebral white matter of MS patients lack β_2 adrenergic receptors. It is this defect on astrocytes that may lead to the pathology of MS, since it confers upon astrocytes the attributes necessary for them to act as immunocompetent antigen-presenting cells (APCs). *In vitro* studies show that astrocytes are capable of processing and presenting myelin basic protein (MBP) and myelin proteolipid protein (PLP) epitopes to T-cells. Immunohistochemical studies have evinced that reactive astrocytes in active MS plaques express the necessary attributes to act as antigen-presenting cells, including the adhesion molecules ICAM-1, VCAM-1 and E-selectin, MHC class-II molecules and B7-1 and B7-2 co-stimulatory molecules. This function of astrocytes as facultative antigen-presenting cells may allow for their participation in tissue destruction. It is normal for norepinephrine to inhibit astrocytic expression of pro-inflammatory cytokines such as TNF-α and IL-1β *via* activation of β_2 adrenergic receptors. However, the lack of the latter in astrocytes may obviously facilitate the synthesis and release of cytokines that are essential in the inflammatory process (inducing chemokines, adhesion molecule induction, activation of T and B cells and microglia), but are also involved in the destruction of myelin and oligodendrocytes (Keyser et al. 2004). The aforementioned lack of receptors may also lead to high-level iNOS expression by astrocytes in MS plaques (Liu et al. 2001). The iNOS isoform produces substantial amounts of NO; as well as free-radicals, which can directly or indirectly cause oligodendrocyte injury, demyelination, impairment of axonal dysfunction and axonal damage. Moreover, the lack of β_2 adrenergic receptors on astrocytes may also direct the induction of astrogliosis through inhibition of cell-cycle progression, preventing the expression of such regulatory molecules as cdk1, cdk2 and cyclin-regulated protein kinases.

Whereas astrocytes normally produce a variety of trophic factors like neuregulin, NGF and BDNF, in MS this production may be impaired by the said lack of β_2 adrenergic receptors. Neuregulin – a very important differentiation and survival factor as regards oligodendrocytes – is on the decline in the astrocytes of active MS plaques. BDNF and NGF are also essential survival factors if oligodendrocytes and neurons are concerned, so any diminution may lead to demyelination, and then to the damage and death of oligodendrocytes, thereby potentially contributing to the neurodegenerative process. Yet another impairment caused by the lack of the β_2 adrenergic receptors is a disrupted stimulation of astrocytic glycogenolysis. In situations of increased neuronal activity, the axonal energy supply is not sufficient to prevent the degeneration of axons (axonopathy) and progressive axonal loss (Keyser et al. 2004).

In MS astrocytes seem to play dual roles of destruction and protection. Activated astrocytes secrete IL-10, which acts as an anti-inflammatory cytokine. IL-10 inhibits microglia antigen presenting function, T cell proliferation and cytokine synthesis by $CD4^+$ T cells. Other protective effects of astrocytes in the pathogenesis of MS include inhibition of NO production by activated microglia and secreting TGF-β that induce microglia cell apoptosis.

ASTROCYTES IN THE AGING BRAIN

Glial cells derived from an aged brain retain all the glial phenotypes present in early development, and these cells are at various stages of maturation. Immature astrocytes in the aging brain would seem to respond to signals from the microenvironment (Minagar et al. 2002), including neuronal signals, and differentiate into mature astrocytes, but in special conditions such as brain insult react through astrogliosis (Vernadakis et al. 1995). In the course of aging, immature glial cells proliferate, not only in response to neuronal injury (reactive gliosis), releasing glial factors essential for regeneration (Minagar et al. 2002).

The glial changes of normal brain aging have largely been since glial activation has been deemed of lesser importance than neuron degeneration. Finch has studied the activation of astrocytes during normal aging, using a glial fibrillary acidic protein (GFAP) as a marker (Finch 2003). GFAP expression (mRNA and protein) increases progressively in the course of human aging. While the cell volume of the astrocyte compartment increases, the changes in numbers of astrocytes with aging are insignificant. Increases in GFAP transcription with age are hypothesized to reflect an increased quantity of oxidatively-damaged proteins.

The increasing expression of GFAP during aging is considered secondary to neurodegeneration. However, it may be crucial where diminishing synaptic function is concerned. It seems to be a relationship between astrocyte activity over time and some neuronal functions which are modified by both types of cells. Astrocytes can modify synaptic activity by controlling local neurotransmitter concentrations (Finch 2003).

Recently the researchers have gained an insight into key pathological features associated with Alzheimer's disease, such as the Aβ plaques or neurofibrillary tangles that are to be seen in brains from cognitively normal elderly individuals. The difference is that amyloid deposition is not progressive in normal aging and the plaques may be subject to turnover. They can also be the early signals for Alzheimer's disease, because the increasing density of amyloid deposits can give rise to cognitive impairment.

Normal aging in the human brain is accompanied by not only an increased incidence of astrocyte and microglia activation, but also by neuronal abnormalities. Advancing age is correlated with increased cerebral cortical expression of S100β protein and mRNA. This increase is rather a beneficial response to aging known to promote neuronal survival and neurite growth. On the other hand, the increases in S100β levels with aging may also increase susceptibility to pathological processes collectively referred to as S100β over-expression. The neurite growth-promoting effects of S100β can change the non-neuritic form of the Aβ deposits to the pathogenic neuritic forms typical of AD (Mrak and Griffin 2005).

The aging brain is in an environment different from that impinging upon the young adult brain, in terms of the types and intensities of signals produced and the ability to respond to such signals. Environmental changes in the aging brain are likely to have a large impact on the functioning of the NSC with age. With aging, there is a decline in the brain's capacity to produce new neurons in the neurogenic regions. Interestingly, there is some evidence that age-related impairment may not be due to the effects on the NSC themselves, but is rather imposed by environmental conditions (Song et al. 2002b). The fact that the mature CNS is an unfavorable environment for neuronal regeneration is largely a result of the presence there of growth inhibitory factors, and the limitation of growth-factor release by astrocytes (Limke and Rao 2003). This may complicate any attemps to use stem cells for therapy in the aging brain.

CONCLUSIONS

Traditionally, astrocytes were perceived to be passive elements in the brain, offering structural, metabolic and trophic support to the neurons. Recent years have changed that view: it has been documented that that astrocytes are dynamic regulators of neuronal activity and signal transmission. They play a role in neuronal development, activity, plasticity, differentiation and maturation. Astrocytes produce growth factors that can regulate the neuronal microenvironment. They are also capable of controlling CNS synapses, and are active participants in synaptic transmission. Astrocytes can promote neurogenesis by instructing stem cells to adopt the neuronal fate and promoting their proliferation. Astrocytes also play a major role in brain pathology. Astrocyte hypertrophy, the accumulation of GFAP and reactive gliosis are pathological features characteristic of the aging-related pathologies that can be observed in neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, and normal brain aging. The described spectrum of astrocytic responses at various stages of different brain diseases demonstrates the importance of these cells where knowledge of neurological disorders is concerned.

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REFERENCES

Anderson MF, Blomstrand F, Blomstrand Ch, Eriksson PS, Nilsson M (2003) Astrocytes and stroke: Networking for Survival? Neurochem Res 2: 293–305.

Ayata C, Ropper AH (2002) Ischemic brain oedema. J Clin Neurosci 9: 113–124.

Barbeito LH, Pehar M, Cassina P, Vargas MR, Peluffo H, Viera L, Estevez AG, Beckman JS (2004) A role of astrocytes in motor neuron loss in amyotrophic lateral sclerosis. Brain Res Rev 47: 263–274.

Bezzi P, Volterra A (2001) A neuron-glia signalling network in the active brain. Curr Opin Neurobiol 11: 387–394.

Budd SL, Lipton SA (1998) Calcium tsunamis: Do astrocytes transmit cell death messages *via* gap junctions during ischemia? Nat Neurosci 1: 431–432

Chen Y, Vartiainen NE, Ying W, Chan PH, Koistinaho J, Swanson RA (2001) Astrocytes protect neurons from nitric oxide toxicity by a glutathione-dependent mechanism. J Neurochem77: 1601–1610

Compston A, Coles A (2002) Multiple sclerosis. Lancet 359: 1221–1231

Cotrina ML, Kang J, Lin JH, Bueno E, Hansen TW, He L, Liu Y, Nedergaard M (1998) Astrocytic gap junctions remain open during ischemic conditions. J Neurosci 18: 2520–2537

Dervan AG, Meshul ChK, Beales M, McBean GJ, Moore C, Totterdell S, Snyder AK, Meredith GE (2004) Astroglial plasticity and glutamate function in a chronic mouse model of Parkinson's disease. Exp Neurol 190: 145–156

De Vitt VA, Perry G, Cohen M, Silver J (1998) Astrocytes regulate microglial phagocytosis of senile plaque cores of Alzheimer's disease. Exp Neurol 149: 329–340

Dong Y, Benveniste EN (2001) Immune function of astrocytes. Glia 36: 180–190.

Dringen R, Pfeiffer B, Hamprecht B (2002) Synthesis of the antioxidant glutathione in neurons: Supply byby astrocytes of CysGly as precursor for neuronal glutathione. J Neurosci 19: 562–569.

Duffy S, MacVicar BA (1995) Adrenergic calcium signaling in astrocyte networks within the hippocampal slice. J Neurosci 15: 5535–5550.

Ekdahl ChT, Claasen J-H, Bonde S, Kokaia Z, Lindvall O (2003) Inflammation is detrimental for neurogenesis in adult brain. Proc Natl Acad Sci U S A 10023: 13632–13637.

Finch CE (2003) Neurons, glia and plasticity in normal brain aging. Neurobiol Aging 24: S123–S127.

Gruol DL, Nelson TE (1997) Physiological and pathological roles of interleukin-6 in the central nervous system. Mol Neurobiol 15: 307–339.

Hagberg A, Qu H, Saether O, Unsgard G, Haraldseth O, Sonnewald U (2001) Differences in neurotransmitter synthesis and intermediary metabolism between glutamatergic and GABA-ergic neurons during 4 hours of middle cerebral artery occlusion in the rat: The role of astrocytes in neuronal survival. J Cereb Blood Flow Metab 21: 1451–1463.

Haydon PG (2000) Neuroglial networks: Neurons and glia talk to each other. Curr Biol 10: R712–R714.

Holroyd S, Shepherd ML (2001) Alzheimer's disease: A review for the ophthalmologist. Surv Ophthalmol 45: 516–524.

John GR, Lee SC, Brosnan CF (2003) Cytokines: Powerful regulators of glial cell activation. Neuroscientist 9: 10–22.

Johnstone M, Gearing AJ, Miller KM (1999) A central role for astrocytes in the inflammatory response to beta-amyloid; chemokines, cytokines and reactive oxygen species are produced. J Neuroimmunol 93: 182–193.

Kalaria RN (1999) Microglia and Alzheimer's disease. Curr Opin Hematol 6: 15–24.

Kang J, Jiang L, Goldman SA, Nedergaard M (1998) Astrocyte-mediated potentiation of inhibitory synaptic transmission. Nat Neurosci 1: 683–692.

Keyser J, Zeinstra E, Wilczak N (2004) Astrocytic $ß_2$-adrenergic receptors and multiple sclerosis. Neurobiol Dis 15: 331–339.

Kielan T, Drew PD (2005) Cytokines of the nervous system. In: Inflammatory Disorders of the Nervous System (Minagar A, Alexander JS, eds). Humana Press, Totowa, NJ

Környei Z, Szlavik V, Szabo B, Gócza E, Czirók A, Madarasz E (2005) Humoral and contact interactions in astroglia/stem cell co-cultures in the course of glia-induced neurogenesis. Glia 49: 430–444.

Kurt MA, Davies DC, Kidd M (1999) ß-amyloid immunoreactivity in astrocytes in Alzheimer's disease brain biopsies: An electron microscope study. Exp Neurol 158: 221–228.

Liberto ChM, Albrecht PJ, Herx LM, Yong VW, Levison SW (2004) Pro-regenerative properties of cytokine-activeted astrocytes. J Neurochem 89: 1092–1100.

Limke T, Rao MS (2003) Neural stem cell therapy in the aging brain: Pitfalls and possibilities. J Hematother Stem Cell Res 12: 615–623.

Lin JH, Weigel H, Cotrina ML, Liu S, Bueno E, Hansen AJ, Hansen TW, Goldman S, Nedergaard M (1998) Gap-junction-mediated propagation and amplification of cell injury. Nat Neurosci 1: 494–500.

Liu JS, Zhao ML, Brosnan CF (2001) Expression of inducible nitric oxide synthase and nitro tyrosine in multiple sclerosis lesions. Am J Pathol 158: 2057–2066.

Martineau M, Baux G, Mothet JP (2006) D-serine signalling in the brain: Friend or foe. Trends Neurosci 29: 481–491.

Miller A, Glass-Marmor L, Abraham M, Grossman I, Shapiro S, Galboiz Y (2004) Bio-markers of disease activity and response to therapy in multiple sclerosis. Clin Neurol Neurosurg 106: 249–254.

Minagar A, Shapshak P, Fujimura R, Ownby R, Heyes M, Eisdorfer C (2002) The role of macrophage/microglia and astrocytes in the pathogenesis of three neurological disorders: HIV-associated dementia, Alzheimer disease and multiple sclerosis. J Neurol Sci 202: 13–23.

Mothet JP, Pollegioni L, Ouanounou G, Martineau M, Fossier P, Baux G (2005) Glutamate receptor activation triggers a calcium-dependent and SNARE protein-dependent release of the gliotransmitter D-serine. Proc Natl Acad Sci U S A 102: 5606–5611.

Mrak RE, Griffin WST (2001) The role of activated astrocytes and of the neurotrophic cytokine S100β in the pathogenesis of Alzheimer's disease. Neurobiol Aging 22: 915–922.

Mrak RE, Griffin WST (2005) Glia and their cytokines in progression of neurodegeneration. Neurobiol Aging 26: 349–354.

Nagatsu T, Mogi M, Ichinose H, Togari A (2000) Changes in cytokines and neurotrophins in Parkinson's disease. J Neural Transm Suppl 60: 277–290.

Nagele RG, Andrea MRD, Lee H, Venkataraman V, Wang H-Y (2003) Astrocytes accumulate Aß 42 and give rise to astrocytic amyloid plaques in Alzheimer disease brains. Brain Res 971: 197–209.

Nakayama T, Momoki-Soga T, Inoue N (2003) Astrocyte-derived factors instruct differentiation of embryonic stem cells into neurons. Neurosci Res 46: 241–249.

Nedergaard M, Ransom B, Goldman SA (2003) New roles for astrocytes: Redefining the functional architecture of the brain. Trends Neurosci 26: 523–530.

Norenberg MD (2005) The Reactive Astrocyte. In: The Role of Glia in Neurotoxicity (Ashner M, Costa LG, eds). CRC Press Boca Raton, Washington DC, p. 73–92.

Pehar M, Cassina P, Vargas MR, Castellanos R, Viera L, Beckman JS, Estévez AG, Barbeito L (2004) Astrocytic production of nerve growth factor in motor neuron apoptosis: Implications for amyotrophic lateral sclerosis. J Neurochem 89: 464–473.

Petersen A, Mani K, Brundin P (1999) Recent advances on the pathogenesis of Huntington's disease. Exp Neurol 157: 1–18.

Ridet JL, Malhotra SK, Privat A, Gage FH (1997) Reactive astrocytes: Cellular and molecular cues to biological function. Trends Neurosci 20: 570–577.

Rogers J, Lue LF (2001) Microglial chemotaxis, activation and phagocytosis of amyloid ß-peptide as linked phenomena in Alzheimer's disease. Neurochem Int 39: 333–340.

Rouach N, Avignone E, Meme W, Koulakoff A, Venance L, Blomstrand F, Giaume C (2002) Gap junctions and connexin expression in the central nervous system. Biol Cell 94: 457–475.

Samii A, Nutt JG, Ransom BR (2004) Parkinson's disease. Lancet 363: 1783–1793.

Schipke CG, Kettenman H (2004) Astrocyte responses to neuronal activity. Glia 47: 226–232.

Schipper HM (1996) Astrocytes, brain aging and neurodegeneration. Neurobiol Aging 17: 467–480.

Schmalenbach C, Műller HW (1993) Astroglia-neuron interactions that promote long-term neuronal survival. J Chem Neuroanat 6: 229–237.

Schubert P, Ogata T, Marchini C, Ferroni S (2001) Glia-related pathomechanisms in Alzheimer's disease: A therapeutic target? Mech Aging Dev 123: 47–57.

Shelton MK, McCarthy KD (2000) Hippocampal astrocytes exhibit Ca^{2+}-elevating muscarinic cholinergic and histaminergic receptors *in situ*. J Neurochem74: 555–563.

Shyam DR, Hong Z, Weiss JH (2003) Disruption of glial glutamate transport by reactive oxygen species produced in motor neurons. J Neurosci 23: 2627–2633.

Simic G, Lucassen PJ, Krsnik Z, Kruslin B, Kostovic I, Winblad B, Bogdanovic (2000) nNOS expression in reactive astrocytes correlates with increased cell death-related DNA damage in the hippocampus and entorrhinal cortex in Alzheimer' disease. Exp Neurol 165: 12–26.

Singhrao SK, Neal JW, Morgan BP, Gasque P (1999) Increased complement biosynthesis by microglia and complement activation on neurons in Huntington's disease. Exp Neurol 159: 362–376.

Song H, Stevens CF, Gage FH (2002a) Astroglia induce neurogenesis from adult neural stem cells. Nature 417: 39–44.

Song H, Stevens CF, Gage FH (2002b) Neural stem cells from adult hippocampus develop essential properties of functional CNS neurons. Nat Neurosci 5: 438–445.

Strong MJ (2003) The basic aspects of therapeutics in amyotrophic lateral sclerosis. Pharmacol Ther 98: 379–414.

Tuppo EE, Arias HR (2005) The role of inflammation in Alzheimer's disease. Int J Biochem Cell Biol 37: 289–305.

Ullian EM, Sapperstein SK, Christopherson KS, Barres BA (2001) Control of synapse number by glia. Science 291: 657–660.

Unsicker K, Strelau J (2000) Functions of transforming growth factor-beta isoforms in the nevous system. Cues based on localization and experimental *in vitro* and *in vivo* evidence. Eur J Biochem 267: 6972–6975.

Vernadakis A, Kentroti S, Kazazoglou T, Lambropoulos EF, Geladopoulos T, Stefanis C (1995) Plasticity of astrocytes in aging. Eur Neuropsychopharmacol 5: 222–223.

Vernadakis A, Lambropoulos E (2000) Cell culture as a model to study cell-cell interactions during development aging and neurodegenerative diseases. Int J Dev Neurosci 18: 139–143.

Vesce S, Bezzi P, Volterra A (1999) The active role of astrocytes in synaptic transmission. Cell Mol Life Sci 56: 991–1000.

Villegas SN, Poletta FA, Carri NG (2003) Glia: A reassessment based on novel data on the developing and mature central nervous system. Cell Biol Int 27: 599–609.

Vincent VA, Tilders FJ, Van Dam AM (1997) Inhibition of endotoxins-induced nitric oxide synthase production in microglial cells by the presence of astroglial cells: A role for transforming growth factor beta. Glia 19: 190–198.

Viviani B, Marinovich M (2005) Cytokines in neuronal – glia interaction. In: The role of glia in neurotoxicity (Ashner M, Costa LG, eds). CRC Press Boca Raton, Washington DC, p.125–140.

Wegiel J, Wang KC, Tarnawski M, Lach B (2000) Microglial cells are the driving force in fibrillar plaque formation, whereas astrocytes are a leading factor in plaque degradation. Acta Neuropathol 100: 356–364.

Wolosker H, Panizzutti R, De Miranda J (2002) Neurobiology through the looking-glass: D-serine as a new glial-derived transmitter. Neurochem Int 41: 327–332.

Xiao B-G, Link H (1999) Is there a balance between microglia and astrocytes in regulating Th1/Th2-cell responses and neuropathologies? Immunol Today 20: 477–479.

Zeinstra E, Wilczak N, Keyser J (2003) Reactive astrocytes in chronic active lesions of multiple sclerosis express co-stimulatory molecules B7-1 and B7-2. J Neuroimmunol 135: 166–171.

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