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Review

Some aspects of astroglial functions and aluminum implications for neurodegeneration

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ABSTRACT

The present decade had witnessed an unprecedented attention focused on glial cells as a result of their unusual physiological roles that are being unraveled. It is now known that, rather than being a mere supporter of neurons, astroglia are actively involved in their modulation. The aluminum hypothesis seems to have been laid to rest, probably due to contradictory epidemiological reports on it as a causative factor of neurodegenerative diseases. Surprisingly, newer scientific evidences continue to appear and recent findings have implicated astrocytes as the principal target of its toxic action. In view of the likely detrimental effects of the interaction between these two infamous partners in neuroscience on neurons and nervous system, we have reviewed some aspects of glia–neuron interaction and discussed the implications of aluminum-impaired astrocytic functions on neurodegeneration. Because sporadic causes still account for the majority of the neurodegenerative diseases of which Alzheimer's disease is the most prominent, it has been suggested that neurotoxicologists should not relent in screening for the environmental agents, such as aluminum, and that considerable attention should be given to glial cells in view of the likely implications of environmental toxicants on their never-imagined newly reported roles in the central nervous system (CNS).

Contents

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1. Introduction

It is not only surprising but puzzling too that a predominant cell type in the brain such as glia, constituting more than 50% of the total cell count and outnumbering neurons 10-fold, could be considered for several decades to provide only mere passive support to neurons and the overall function of the nervous system. One of the reasons glial cells have been neglected is that they do not generate electrical pulses, an important parameter in experimental techniques of neurobiology. Another reason why neuroscientists failed to detect signaling among glia according to Fields (Fields and Stevens-Graham, 2002) is partly because they had insufficient analytical technology, but primarily because they were looking in the wrong place. Instead of electrical ones, glia rely on chemical signals to convey messages. Recent advances in neuroscience had greatly expanded the relationship between neurons and glia, and this has however become a challenge to traditional neurobiology. In fact, Haydon (2001) had called for the redrawing of the classic picture of the synapse to include the glia surrounding the junction between two neurons as the third member of a 'tripartite synapse'. It is now known that astrocytes play a critical role in several aspects of signal transmission as well as synaptic plasticity and that defects in these functions may lead to neurodegeneration (Rothstein et al., 1996; Theiss and Meller, 2002; Ullian et al., 2004) (for review, see Anderson and Swanson, 2000; Sonnewald et al., 2002).

Aluminum is a prominent environmental factor, but, unfortunately, the majority of works on the toxic effects of aluminum have involved an examination of the direct effects of aluminum on neuronal cells while works on the toxic effects of aluminum on astrocytes are lagging behind (Aremu and Meshitsuka, 2005; Guo and Liang, 2001). Aluminum hypothesis states that aluminum in certain chemical forms is deleterious and is a cofactor in the etiology of at least some forms of mental impairment and, more specifically, of Alzheimer's disease (AD). This hypothesis has been a subject of unprecedented controversy since epidemiological reports are contradictory (Forbes and McLachlan, 1996; Forster et al., 1995; Jacqmin et al., 1994; Rondeau et al., 2000). Unlike many infectious diseases where the consequences of exposure are readily apparent, in chronic diseases, a cause-and-effect relationship is frequently difficult to prove, particularly for associations involving environmental risk factors (Forbes and Gentleman, 1998). In spite of the controversy surrounding the aluminum hypothesis, there is a mounting scientific evidence suggesting a relationship between the neurotoxicity of aluminum and the pathogenesis of AD. In the present work, we have tried to review some new aspects of glia–neuron interaction and discuss the implications of aluminum-impaired astrocytic function on neurodegeneration.

2. Neuron–glia communication and intersynaptic cross-talk

Evidence has accumulated in support of bi-directional communication between neurons and glia. The bi-directional communication is necessary for axonal conduction, synaptic transmission, and information processing. Glial cells respond to various electrical, mechanical, and chemical stimuli, including neurotransmitters, neuromodulators, and hormones, with an increase in intracellular Ca^{2+} concentration (for review, see Verkhratsky et al., 1998). In fact, different molecules released by neurons can affect intracellular Ca^{2+} levels in glial cells while the neurotransmitter released by astrocytes can modulate synaptic transmission, giving rise to the concept of 'tripartite synapses' (for review, see Haydon, 2001). The signals between neurons and glia include ion fluxes; neurotransmitters, particularly glutamate; cell adhesion molecules (CAMs), including Ng-CAM, NCAM, N-cadherin, and integrin $\beta 1$; and specialized signaling molecules like sex steroids and cAMP released from synaptic and nonsynaptic regions of the neuron (Fields and Stevens-Graham, 2002; Marchetti, 1997; Neugebauer et al., 1988; Grumet and Edelman, 1984; Ullian et al., 2001). Responding to stimuli, increased levels of calcium in adjacent astroglia evoke the release of the excitatory neurotransmitter glutamate, thereby enhancing the activity of the synapses formed by neighboring neurons, the calcium waves can also propagate through many astroglia and regulate synapses over wide areas by means of gap junction. It has been proposed that such glial Ca^{2+} waves may constitute an extraneuronal signaling pathway in the central nervous system (Hirase et al., 2004; Newman and Zahs, 1997). Propagation of interastrocyte Ca^{2+} waves is now known to be mediated by diffusion of extracellular adenosine triphosphate (ATP) and may require regenerative release of ATP, i.e., ATP-induced ATP release (Anderson et al., 2004).

It is interesting however that not only were neurons communicating with glia and glia sending signals among themselves but new findings show that astroglia regulate intersynaptic cross-talks (i.e., interactions between independent synaptic inputs) and possibly the overall volume transmission in the brain by influencing the diffusion in the extracellular space (Piet et al., 2004). The present observation was based on the fact that reduced astrocytic coverage of magnocellular neurons occurring in the supraoptic nucleus (SON) of lactating rats facilitates diffusion in the extracellular space (ECS), as revealed by tortuosity and volume fraction measurements. This is consistent with the fact that astrocytic coverage of SON neurons in the hypothalamus significantly diminishes in conditions of increased oxytocin secretion, like lactation (Theodosis and Poulain, 1993). This can be explained by the fact that reduced astrocytes not only limit the re-uptake of most of the released transmitter (in this case oxytocin) but

also minimize the hindrance to diffusion in the ECS (Roitbak and Sykova, 1999; Rusakov and Kullmann, 1998; Sykova, 2001) thereby facilitating the neurotransmitter action in regulating intersynaptic communication (Piet et al., 2004).

3. Astroglia and glutamate clearance

Considering the abundance of glutamate in the brain and possible lack of its extracellular conversion, brain tissue needs a very high glutamate uptake activity. The transporter proteins represent a very significant mechanism for removal of glutamate from ECS, and their importance for the long-term maintenance of low and non-toxic concentrations of glutamate is now well documented (Danbolt, 2001). It is important to remember that the functional activity of the brain is primarily composed of interplay between excitation and inhibition and the prevailing mediating neurotransmitters are respectively glutamate and GABA. Schousboe (2003) has described the role of astrocyte in regulating the glutamatergic and GABAergic neurotransmission for excitatory and inhibitory activities in a review. We have focused on glutamate clearance in the present review in line with its scope.

Glial cells constitute 90% of cells in the human nervous system (Ullian et al., 2001), and glial glutamate transporter molecules have been quantified to be about 15,000 and 21,000 per mm^3 tissue in the stratum radiatum of hippocampus CA1 and the molecular layer of cerebellum respectively (Lehre and Danbolt, 1998). It is not surprising, therefore, that glial glutamate transporters provide the majority of functional glutamate transport and are essential for maintaining low extracellular glutamate and for preventing chronic glutamate neurotoxicity (Rothstein et al., 1996). This may explain why astrocytic wrapping of neurons, therefore, contributes to the regulation of synaptic efficacy in the central nervous system by regulating the level of glutamate in the ECS (Oliet et al., 2001). Reduced astrocytic coverage of SON neurons in lactating rats leads to a glutamate clearance deficiency, resulting in enhanced glutamate concentration in the ECS and increased activation of presynaptic metabotropic glutamate receptors (mGluRs) and inhibition of glutamate release (Oliet et al., 2001). Thus, the enhanced glutamate concentration is controlled by the activation of the mGluRs so as to prevent excessive accumulation of glutamate that may compromise neuronal survival. It is not known whether the reduced glial population observed in lactating rats is solely due to hormonal effect or in part influenced by glutamate concentration. However, release of glutamate as well as the densities of both glutamate transporters and receptors is partly regulated by glutamate itself (Perkinton and Sihra, 1999; Sanchez-Prieto et al., 1996).

Astrocytic volume and synapse density are also known to fluctuate in the rat hippocampus with the estrous cycle (Desmond and Levy, 1998; Klintsova et al., 1995; Woolley and McEwen, 1992), and as noted in the preceding section, astrocytic coverage of SON neurons in the hypothalamus significantly diminishes during lactation. These observations may explain gender disparity in many neurodegenerative conditions, including Parkinson's disease, AD, cerebral ischemia, traumatic brain injury, epilepsy, Huntington's chorea, and amyotrophic lateral sclerosis (ALS) that have been linked to disturbed glutamate homeostasis (Maragakis and Rothstein, 2004; O'Shea, 2002). For instance, several studies suggested that women are at higher risk of dementia than men (Ruitenberg et al., 2001), but men with AD had an increased risk of mortality relative to women (Lapane et al., 2001). On the other hand, Parkinson's disease is more prevalent in men than women. Thus, while reduced re-uptake of dopamine as a result of reduced astrocytic coverage of neurons may relieve Parkinson's disease in women, it may not be so in case of reduced re-uptake of glutamate that may favor neuronal death as in AD. Although, astrocytes are capable of transporting dopamine (Takeda et al., 2002; Inazu et al., 1999), it is not known to what extent the reduced astrocytic coverage of neurons will affect dopamine re-uptake. Moreover, while caffeine consumption generally reduces Parkinson disease in men, this hypothetical beneficial effect may be prevented by use of estrogen replacement therapy in women (Ascherio et al., 2004). Further research is therefore necessary to shed more light on interrelationships of sex hormones, regional neuron–glia population ratio, neurotransmitter clearance, and neurodegenerative diseases. Nevertheless, underlying mechanisms for neurodegenerative diseases in men and women may not be generalized.

4. Astroglia as a reservoir of neurotrophic factor

Neurotrophins are proteins that bind to neurons, triggering intracellular signals that culminate in survival, growth, or the modulation of neuronal function (Reichardt, 2003). The existence of dopaminergic neurotrophic activity in conditioned media derived from primary glial cells (O'Malley et al., 1992) and from several cell lines with the properties of glia (Engele et al., 1991) has been established. Lin et al. (1993) had subsequently cloned the glial-cell-line-derived neurotrophic factor (GDNF). Other investigators have reported the protective role of GDNF against various toxicities in vivo (Tomac et al., 1995) or in vitro (Eggert et al., 1999) as well as prevention or delay of degeneration or death of dopaminergic neurons (Beck et al., 1995; Sauer et al., 1995) and motor neurons (Oppenheim et al., 1995; Yan et al., 1995) including its functional recovery effect in parkinsonian monkeys (Gash et al., 1996). However, recent findings suggest that glial cells (astroglial and Schwann cells) could act as a reservoir of brain-derived neurotrophic factor (BDNF) to promote the growth and maturation of adjacent neurons (Alderson et al., 2000; Reichardt, 2003) by employing truncated receptor tyrosine kinase (Trk)-B, which promotes internalization and subsequent release of BDNF (Alderson et al., 2000). Rose et al. (2003) have recently shown that astrocytes predominantly express TrkB-T1 (TrkB lacking kinase) and respond to brief application of BDNF by releasing calcium from intracellular stores. They thus described a novel mechanism of neurotrophin action in the brain and concluded that TrkB-T1 has a direct signaling role in mediating calcium release from astrocytes. BDNF is released by neurons, and it is present in the brain at sub-nanomolar concentrations required to generate calcium waves. Reichardt (2003) therefore suggested that BDNF might be a means by which neurons

signal to glia that respond by generating calcium waves. The implications of calcium waves have been discussed in the preceding section.

5. Induction of blood–brain barrier (BBB) by astroglia

Astrocytes were once thought to form the physical basis of the restrictive BBB due to the extension of their foot processes that surround CNS microvessels. However, contemporary studies with endothelial cell and astrocyte co-cultures, though maintain that astrocytes are responsible for the induction of tight junctions (Abbott, 2002; Janzer and Raff, 1987), refute the dogma that astrocytes themselves form the physical barrier between the blood vessels and the brain parenchyma (Yang and Aschner, 2003). Nevertheless, primary astrocytes can induce BBB characteristics such as high electrical resistance and reduced paracellular permeability when co-cultured with cerebral brain endothelial (Abbott, 2002). The extension of astrocyte projections to the BBB is now known to be responsible for its maturation by integrating signaling networks necessary for BBB development and maintenance (Lee et al., 2003; Rieckmann and Engelhardt, 2003). Surprisingly, the ability of astrocytes to induce tight junction is not limited to brain vascular endothelial cells alone. Hayashi et al. (1997) reported that, through contact with their feet, astrocytes are capable of transdifferentiating non-neural endothelial cells into the brain type, endowing them with the BBB properties.

Although the endothelial cells form the barrier proper, interaction with adjacent cells is required for barrier maintenance, a prerequisite for brain homeostasis and proper neural function. When endothelial cells were cultured alone, tight junctions appear fragmentary, but when co-cultured with astrocytes, the length, breath, and the complexity of the junctions are increased, closely resembling their counterparts in vivo (Tao-Cheng et al., 1987). This has been corroborated by the recent work of Hamm et al. (2004) where brain endothelial cells in co-culture with astrocytes form a tight permeability barrier for ^{3}H-inulin and ^{14}C-sucrose. Removal of astrocytes from the co-culture resulted in an increased permeability to small traces across the brain endothelial cells monolayer and an opening of the tight junctions to horseradish peroxidase as detected by electron microscopy. Strikingly, the opening of BBB tight junctions in the absence of astrocytes was not accompanied by the loss of the junctional localization of tight junction proteins characteristic of pathological conditions accompanied by BBB breakdown. Thus, astrocytes' presence at BBB may only be functionally relevant to the efficacy of BBB rather than physically contributing to it, nevertheless, they are indispensable.

6. Astroglia role in amyloid beta (Aβ) degradation

A pathological hallmark of AD is the senile plaque, containing Aβ fibrils, microglia, and astrocytes (El Khoury et al., 1996). It is known that Aβ fibrils promote neurite outgrowth and exert a cytotoxic effect on neurons by promoting microglial activation, thereby generating reactive oxygen intermediates and inducing cytotoxic cellular oxidative stress (El Khoury et al., 1996; Yan et al., 1996). More recently, it has been shown that the dementia caused by Aβ deposit may be due to its enhancement of glial glutamate uptake, thereby attenuating synaptic efficacy (Ikegaya et al., 2002). Despite the fact that activated microglia are known to produce neurotoxin, the same microglia were assumed to be responsible for the clearance of Aβ in some earlier reports (Paresce et al., 1996; Shaffer et al., 1995), while there was no defined role assigned to astrocytes surrounding amyloid plaques. The recent work of Wyss-Coray et al. (2003) showed that astrocytes present around amyloid plaques not only adhere to and immobilized by Aβ, but also degrade it. However, only adult astrocytes degrade Aβ efficiently. It is very interesting that their findings also showed that the adult astrocytes, in contrast to microglia, do not require additional stimuli such as opsonins or cytokines to be able to remove and degrade Aβ. A study by Koistinaho et al. (2004) now shows that ApoE seems to be important in the degradation and clearance of deposited Aβ species by astrocytes.

There is accumulated evidence that factors regulating Aβ catabolism (Carson and Turner, 2002; Iwata et al., 2000), clearance (Morelli et al., 2002; Shibata et al., 2000), and aggregation (Wisniewski et al., 1997; Wolozin, 2004) are critical in regulating its metabolism. Thus, dysregulation of Aβ clearance by astrocytes may precede or be responsible for its accumulation in AD (Guenette, 2003; Koistinaho et al., 2004; Nicoll and Weller, 2003; Wyss-Coray et al., 2003). This is very plausible because it is well known that production of Aβ via APP processing is not the only factor that can influence the probability of Aβ deposition (DeMattos et al., 2001; Frederickson and Brunden, 1994). Zlokovic (2004) has further suggested that understanding Aβ exchanges between brain and blood, and vice versa, and developing transport-based systemic Aβ-lowering strategies may provide new important insights into pathogenesis and therapeutic control of AD.

7. Other protective roles of astroglia

There may be several other ways by which astrocytes protect neurons depending on the nature of the toxic agent. For example, Chen et al. (2001) suggested that astrocytes protect neurons from NO toxicity by a glutathione-dependent mechanism. Neurons in culture with the glutathione-depleted astrocytes exhibited a two-fold increase in cell death over a range of NO donor concentrations. Glutathione is believed to have many functions among which is scavenging of hydrogen peroxide, superoxide, and free radicals, which are important in death signaling pathway. Glutamic acid decarboxylase (GAD)-expressing astrocytes have been shown to increase glutathione synthesis and release with attendant increased antioxidant activity, explaining their ability to protect neurons from various injuries (Lamigeon et al., 2001). Under glucose deprivation, GAD-expressing astrocytes are capable of releasing lactate from glutamate catabolism, and this has been referred to as an interesting strategy to increase neuronal survival under hypoglycemic conditions (Bellier et al., 2000). In another experimental condition, Lian and Stringer (2004) have

also demonstrated in vivo that energy failure in astrocytes increases the vulnerability of neurons to spreading depression and fluorocitrate. Spreading depression is a wave of depolarization that spreads in all direction from the stimulus site followed by a period of reduction in EEG activity (Leaõ, 1944; Somjen, 2005), while fluorocitrate is known to be a selective inhibitor of the astrocytic Krebs cycle (Lian and Stringer, 2004).

8. Impairment of astrocytes functions by aluminum

Recent findings have implicated astrocytes as the principal target for aluminum toxic action (Campbell et al., 2001; Guo-Ross et al., 1999; Rao, 1992; Suarez-Fernandez et al., 1999; Struys-Ponsar et al., 2000). For example, aluminum salt was more toxic to the glioblastoma cells than neuroblastoma cells (Campbell et al., 2001) and aluminum treatment in vivo or in vitro severely impairs astrocyte function (Guo-Ross et al., 1999; Struys-Ponsar et al., 2000). Levesque et al. (2000) however reported that aluminum incorporation and toxicity in both neuronal and glial cells are ligand-specific.

There is paucity of data on direct evidence of the consequence of aluminum-impaired astrocytes on neuronal vulnerability. However, Sass et al. (1993) clearly showed that prior treatment of astrocytes with aluminum impairs the ability of astrocytes to promote neuronal survival, and it was suggested that aluminum may cause astrocytes to: (i) secrete a factor that makes neurons more susceptible to glutamate-induced toxicity; (ii) secrete a neuronotoxic factor in the presence of glutamate; or (iii) reduce secretion of a factor that protects neurons from glutamate excitotoxicity. From other studies, the third reason seems more plausible. Ahlemeyer et al. (2003) have recently shown that activation of astrocytes impairs their ability to protect neurons after excitotoxic injury due to reduction in the release of soluble and heat-sensitive factors. The heat-sensitive factors may be a neurotrophic or nerve growth factor. Nerve growth factor is capable of protecting neurons from glutamate-induced toxicity (Abe and Saito, 1992). Aluminum chloride has been shown to inhibit production of nerve growth factor (NGF) by cultured mouse brain astroglial cells (Kobayashi et al., 1996). However, ethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetate (EDTA) and citrate blocked the inhibitory effect of Al(III) on the NGF production. Thus, citrate like EDTA might have prevented aluminum uptake and, rather than being a candidate for cellular aluminum uptake, may be a major aluminum chelator both in extra- and intracellular fluids in order to detoxify it (Aremu and Meshitsuka, 2005; Meshitsuka et al., 2002b). Other findings have demonstrated that astrocytes also release neurotrophic factors and that this may be the way by which it offers protection to neurons (Alderson et al., 2000; Eggert et al., 1999; Reichardt, 2003; Sauer et al., 1995; Tomac et al., 1995). If such release can be inhibited or blocked by aluminum, this may spell doom for neurons.

It has been suggested that the established communication between neurons and astrocytes in co-culture system makes neurons aware of astrocytes' presence, thereby becoming over-dependent on astrocytes for survival. Thus, pure neuronal culture is able to withstand toxicity than neurons previously co-cultured with astrocytes (Brown, 1999b; Suarez-Fernandez et al., 1999). In other words, when astrocytes in co-culture are by any means compromised, then neurons become susceptible to sub-lethal doses of toxicants than if it were pure neuronal culture. Brown (1999a,b) demonstrated that, on addition of TGF-β1, which compromised astrocytic clearance of glutamate, reduction in resistance to glutamate toxicity as a result of dependence on astrocytes for survival led to a reduction in neuronal survival. While Sass et al. (1993) did not see any difference in glutamate uptake of astrocytes exposed to aluminum citrate, Struys-Ponsar et al. (2000) reported enhanced glutamate uptake in astrocytes exposed to aluminum chloride. Thus, while glutamate uptake is crucial, the increased toxicity of glutamate to neurons co-cultured with compromised astrocytes may not necessarily be due to reduced glutamate uptake alone. Ye and Sontheimer (1998) have reported reduced tolerance of neurons previously cultured in glutamate-depleted media, when exposed to low levels of glutamate found in normal media containing 10% serum.

The reason(s) why prior treatment of astrocytes with aluminum impairs their ability to promote neuronal survival require further investigations. However, aluminum may interfere with any of the ways by which astrocytes protect neurons from toxic injuries and/or modulate the efficacy of neural transmission. Theiss and Meller (2002) had reported that aluminum significantly impaired the gap junctional intercellular communication in cultured astrocytes. Effect of aluminum on cytoskeletal elements was said to be responsible for the observation. This may be a possible way that aluminum may impair the capability of astrocytes to buffer ions and transmitters in the extracellular environment of neurons, and, as a consequence of the limited functionality of the astrocytes, aluminum could affect the physiological activity of neurons (Rothstein et al., 1996; Theiss and Meller, 2002; Ullian et al., 2004).

Suarez-Fernandez et al. (1999) treated mixed cerebellar cultures containing both neurons and astrocytes with aluminum salt and followed the morphological changes in the different cell types in mixed and near pure cultures. Astrocytes accumulated more aluminum than neurons, and aluminum neurotoxicity occurred in neuroglial cultures containing 10% astrocytes but not in near pure neuronal cultures containing 1% astrocytes. This observation may serve as another evidence in support of neuronal over-dependency on astrocytes for survival in co-culture system. Unfortunately, over-accumulation of aluminum by astrocytes impairs their protective roles, which renders neurons vulnerable despite their lesser accumulation of aluminum. Thus, the accumulated aluminum induced degeneration of astrocytes with evidence of DNA fragmentation characteristic of apoptosis. Moreover, staining of aluminum-treated astrocytes with the DNA-binding fluorochrome Hoechst 33258 revealed the typical apoptotic condensation and fragmentation of chromatin. Other investigators, even at lower concentrations of aluminum salts than previously employed, have further confirmed these findings (Aremu and Meshitsuka, 2005; Guo and Liang, 2001). Impairment of astrocytes metabolism was also shown to aggravate aluminum accumulation by astrocyte, and it was suggested that aluminum could compromise astrocytes via

apoptosis. Thus, loss of astrocytic regulatory and supportive roles in CNS (shown in the preceding sections) may be responsible for neurodegeneration such as observed in AD as well as other neurodegenerative diseases. Moreover, aluminum selectively affects astrocytes' viability, and it is probable that astrocytic death precedes that of neurons in neurodegeneration, but this may be obscured by the ability of astrocytes to proliferate and hence replace the lost ones.

9. Concluding remark

As a result of increased interest in astroglial research and better analytical technology, more active roles have been defined for astrocytes and other glial family of cells. It is now known that the astroglial environment of neurons provides not only metabolic but also trophic support for neurons and contributes to local modulation of synaptic efficacy at excitatory inputs by controlling glutamate clearance and represents an important regulator of glutamatergic communication between dependent synapses by setting the parameters of diffusion in the extracellular space. Defects in these functions have been proposed to predispose to neurodegeneration (Aremu and Meshitsuka, 2005). Environmental factors such as aluminum could target astrocytes for their toxic actions, thereby causing defects in astroglial functions. The most prominent among neurodegenerative diseases, AD, is recognized to be over 95% sporadic and not the result of mutations on a single gene, hence, some environmental factors are expected to be etiological (Adams, 1997; Meshitsuka et al., 2002a; Raiha et al., 1997; Ying, 1997). It is therefore high time that the potential environmental agents such as aluminum, which can impair astroglial functions, are identified. Thus, this is another research opportunity or challenge for neurotoxicologists since there are several potential agents in the environment most of which have not been tested on primary astrocytes. Moreover, the likely consequences of different environmental agents on some of the emerging roles of astrocytes in the CNS as reported in recent publications and possible implications of these consequences for neurodegeneration are worth investigating.

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