The glia doctrine: Addressing the role of glial cells in healthy brain ageing

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1. Introduction

Cognitive frailty is emerging as one of the greatest health challenges of the twenty-first century. As life expectancy of the population increases, the prevalence of cognitive decline, Alzheimer’s disease (AD) and other forms of dementia is also increasing. Nearly 50% of adults over the age of 85 living in industrialised countries are thought to suffer from some form of dementia. The most significant non-modifiable risk factor for cognitive decline and AD in older adults is age itself. In addition, even healthy ageing entails some cognitive impairment that may be modifiable. Therefore, it is critical to understand the basis of ageing-associated cognitive decline, at the molecular, functional and organisational levels, with focus on healthy brain ageing and the most prominent brain diseases.

In the large majority of cases, it is not known whether the primary factors leading to AD are environmental and/or genetic, and more research on brain ageing, AD and other dementias is urgently needed. Recently, research in this area has shifted from an emphasis on the role of neurons, e.g. loss of neurons and structural and functional disruptions, to a broader view including a focus on glial cells. An increasing body of evidence suggests that glial cells play a major role in brain ageing and in several disease processes of the brain. This article summarizes recent advances and emerging hypotheses related to functions of glial cells, with an emphasis on the role of astrocytes.
2. Giall cells: characteristics and complementarity

Giall cells in the brain include astrocytes, oligodendrocytes and microglia. In the gray matter, astrocyte processes make intimate contacts with neurons through perisynaptic processes (Ventura and Harris, 1999), while astrocyte endfeet almost completely ensheathe the blood vessel endothelium (Mathiisen et al., 2010). In the white matter, bundles of myelinated axons are tightly packed, while astrocytes make contact with naked axons at the nodes of Ranvier, and oligodendrocytes generate the myelin sheath. Microglia mediate innate immunity in the brain (Kettenmann et al., 2011) and may play a role in synaptic communication and modulation (Tremblay, 2011).

2.1. Astrocytes

Astrocytes, the most numerous cell type in the human brain, fill most of the space between neurons and blood vessels (Fig. 1A). Recent studies from several laboratories including our own show that astrocytes have strong impact on neuronal function, neuronal development, and brain ageing. Astrocytes regulate extracellular ion concentration, water homeostasis and the acid-base balance in the brain (Amiry-Moghaddam and Ottersen, 2003; Chesler, 2003; Nagelhus and Ottersen, 2013; Papadopoulos and Verkman, 2013). They also actively modulate synaptic transmission by releasing neuroactive compounds. This arrangement with three elements – the presynaptic terminal, the postsynaptic dendrite and the perisynaptic astrocytic process – making a functional unit is referred to as the “tripartite” synapse (for excellent recent reviews see (De Pitta et al., 2011, 2012; Santello et al., 2012). There is bidirectional communication between the neuronal and astrocytic elements: (1) release of transmitters at the synapse can trigger G-protein coupled responses in astrocytes (e.g. through P2Y1 ATP receptors). This can lead to increase in the intra-astrocytic Ca2+ concentration, which in turn stimulates release of signal substances such as glutamate, u-Serine and ATP. (2) It has been shown that astrocytes can feed back to the synapse to control synaptic transmission, either through exocytotic release (Bezzi et al., 2004; Chen et al., 2013; Jourdain et al., 2007) or by channel-mediated release of transmitters (Han et al., 2013a; Lee et al., 2010). Gliotransmitter release from astrocytes can either increase synaptic transmitter release, or decrease it. Adding to the ability of astrocytes to regulate synaptic activity is that different synaptic stimuli could change the morphology of astrocyte perisynaptic processes. By morphologically adapting to changes in the external environment, astrocytes may influence dynamic synaptic plasticity (Oliet et al., 2001; Panatier et al., 2006). However, the role of “gliotransmitter” release in regulating synaptic plasticity is highly debated (Agulhon et al., 2010; Sun et al., 2013).

Astrocyte endfeet form a continuous sheath at the blood-brain barrier (BBB) (Mathiisen et al., 2010) and at interfaces with the cerebrospinal fluid (CSF) (Klika and Antalikova, 1969). Because of

![Fig. 1. Astrocytes and bacterial exosomes.](image-url)
the strategic location of astrocytes, they control movement of all substances across the BBB, act as sensors for changes in pH and the concentration of ions, metabolites and chemicals in the brain, and regulate neuronal activity (Haydon and Carmignoto, 2006), interstitial fluid dynamics (Haj-Yasein et al., 2011; Iliif et al., 2012), regional blood flow (Attwell et al., 2010) and integrity of the BBB (Abbott et al., 2006).

Astrocytes respond to central nervous system (CNS) injury or damage through a process referred to as reactive astroglisis, considered a pathological hallmark/biomarker of CNS structural lesions (Sofroniew and Vinters, 2010). Substantial progress has been made recently in understanding the mechanistic basis of reactive astroglisis as well as the role played by astrocytes in CNS disorders and pathologies. For example, transgenic mouse models have been used to dissect specific aspects of reactive astrogliosis and glial scar formation in vivo. It is now clear that reactive astroglisis is not a simple all-or-none phenomenon but involves a continuum of changes that occur in a context-dependent manner regulated by specific signalling events. These changes include reversible alterations in gene expression, cell hypertrophy with preservation of cellular domains and tissue structure, and long-lasting inflammation and scar formation with rearrangement of tissue structure. Increasing evidence suggests that reactive astroglisis alters normal astrocyte functions, which ultimately play a primary and/or secondary roles in CNS disorders.

Neuronal–glial interactions are complex, and both astrocytes and neurons are coupled together by gap junctions composed of connexins (Giaume and Liu, 2012), and should not only be studied at the level of single cells. The transfer of ions and signalling molecules through gap junctions enable astrocytes to function as a syncytiun. However, cell-cell communication via gap junctions is both dynamic and spatially confined, contrary to some previous models (Giaume and Liu, 2012). Also, connexin isofoms are expressed with regional heterogeneity (Giaume and Liu, 2012). Thus, the properties and plasticity of astrocyte networks must be characterized, before the complex interplay between astrocytes and neurons can be understood (Giaume et al., 2013). Interestingly, the link between astrocytes and autophagy of the lateral sclerosis (ALS), a neurodegenerative disease characterized by motor neuron death, has been emphasized by the discovery of the specific role of super oxide dismutase 1 (SOD1) in astrocyte and motor neuron biology; in particular, a recent report indicates a non-cell-autonomous effect of human SOD1 G37R astrocytes on motor neurons derived from human embryonic stem cells (Marchetto et al., 2008). In mouse models, ALS can be induced by mutations in the gene encoding SOD1, and evidence for the non-cell-autonomous nature of ALS emerged from the observation that wildtype glial cells extended the survival of SOD1 mutant motor neurons in chimeric mice (Marchetto et al., 2008). Also, astrocytes can activate NOX2, leading to high levels of superoxide, an effect that can be reversed by antioxidants, thus providing an assay for drug screening using a human ALS in vitro astrocyte-based cell model.

Human cognitive function, including the capacity for long term potentiation (LTP), declines in older individuals (Hsu et al., 2002), and it is not understood whether and how astrocytes modulate ageing-related cognitive loss. Moreover, it has been proposed that activated microglia can contribute to LTP (Sun et al., 2013) and to age-related decline in LTP (Griffith et al., 2006). However, the discrete roles and specific functions of astrocytes and microglia in the context of ageing are not well defined and remain poorly understood. Recent findings indicate that human glia differentially enhance both activity-dependent plasticity and learning in mice (Han et al., 2013b).

Recent studies strongly support the idea that astrocytes are key players in neurological disease. For example, in an animal model of AD, astroglia undergo general atrophy while astrogliosis is observed surrounding amyloid plaques in early disease stages (Rodriguez et al., 2009). Astrocytes also express amyloid precursor protein (APP) and all the components required for amyloidogenic and non-amyloidogenic processing of APP, including β-site APP-cleaving enzyme 1 (BACE1) and γ-secretase (Grolla et al., 2013; Zhao et al., 2011). APP is the precursor for amyloid Aβ which accumulates together with neurofibrillary tangles and contributes to AD brain pathology. Therefore, it is important to understand the factors that determine the rate at which APP is formed, processed and/or degraded. For example, the expression or function of membrane-bound α, β and γ-secretases, which play a role in APP processing, may be altered in cells from AD patients. Because astroglia also actively produce Aβ, and greatly outnumber neurons, they are likely to make a significant contribution to the Aβ burden in the brain (Grolla et al., 2013; Zhao et al., 2011).

2.2. Astrocyte polarity in health and disease

Astrocyte membranes display distinct domains that form specific interfaces with neuronal synapses and blood vessels, and these features lead to functional and anatomical polarity. It is now understood that polarity of astrocytes and neurons is critical to their normal function and that loss of polarity plays a role in a number of diseases. Pioneering research on astrocytic membrane transporters and channels has revealed that aquaporin-4 (AQP4) and Kir4.1 potassium channels are concentrated in astrocytic membranes abutting blood vessels (Amiry-Moghaddam and Ottersen, 2003; Nagelhus et al., 1999; Nielsen et al., 1997) and demonstrated their roles in brain extracellular water and K+ homeostasis (Amiry-Moghaddam et al., 2003; Haj-Yasein et al., 2011; Thran et al., 2013) (Fig. 1C). We recently showed that loss of astrocyte polarity occurs in AD, epilepsy and stroke (Alvesstad et al., 2013; Eid et al., 2005; Frydenlund et al., 2006; Heuser et al., 2012; Yang et al., 2011). Loss of astrocyte polarity may lead to impaired K+ clearance and hyperexcitability. A similar mechanism may contribute to temporal lobe epilepsy, the increased propensity for seizures after stroke, and the hyperactivity of neurons adjacent to amyloid plaques (Busche et al., 2008). Thus, loss of astrocyte polarity might be a common feature of neurological disease involving astro-degeneration. The role of astrocyte polarity in neuronal and vascular function, BBB integrity, reaction to inflammation, protein aggregation, and transport of nutrients and waste products should therefore be delineated.

2.3. The nature and role of exosomes in glial and bacterial cells

Extracellular vesicles (EVs) are small cell-derived membrane vesicles approximately 100 nm in size released into extracellular space by eukaryotic (exosomes) and prokaryotic cells (outer membrane vesicles, OMVs). EVs have recently attracted interest because of their potential function in cell–cell communication, pathogenesis of several diseases, as possible reservoirs of biomarkers. EVs may also be useful in therapeutic applications including delivery of drugs, vaccines and recombinant plasmids (i.e. gene therapy) (Alvarez-Erviti et al., 2011; Kalra et al., 2012; Thery et al., 2009). Interestingly, the exosome composition may differ depending on their cellular origin. Because EVs can be isolated from most biological fluids, they could become useful sources of next-generation cell-specific biomarkers. For example, neurons and glial cells secrete exosomes that contain proteins and small regulatory RNA (Lachenal et al., 2010). It has also been proposed that astrocytes and other brain cells communicate with each other using exosomal lipid microvesicles to transport peptides and mtDNA (Guescini et al., 2010; Molina-Holgado
and Molina-Holgado, 2010). Exosomes can be taken up by neighbouring neurons and glial cells, facilitating transfer of information and/or pathological proteins to other cells or brain regions. Astrocyte EVs may contain peptides that promote apoptosis and astrogliosis in AD (Wang et al., 2012). However, much remains unknown about the roles played by exosomes in neurons and astrocytes, especially in the intact brain, as opposed to cultured cells (Kalra et al., 2012). The role of the abundantly released OMVs from bacterial cells is also enigmatic (van de Waterbeemd et al., 2013) (Fig. 1D).

2.4. Genome dynamics in brain ageing, inflammation and neurodegeneration

Ageing is the single most important factor linked to dementia. DNA repair capacity may decline with age in a tissue-specific manner and decreased or compromised DNA repair may also contribute to brain ageing (Bishop et al., 2010). Mitochondrial dysfunction with oxidative and nitrosative stress, as well as inflammation, are also potential drivers of age-related disease (Desler et al., 2011; Gredilla et al., 2012). Reactive oxygen species (ROS) and nitrogen species (RNS) damage macromolecules in the cell including DNA, and unrepaired DNA damage can cause epigenetic changes, gene silencing or mutation, and exacerbate other forms of cellular dysfunction in both glial and neuronal cells (Barzilai, 2010). ROS and RNS can also modify lipids and proteins, leading to membrane dysfunction and protein unfolding and aggregation. Defects in DNA repair contribute to normal cellular ageing and neurodegeneration (Bishop et al., 2010; Bohr et al., 2007). Accumulation of this damage in the background of a functional DNA repair response is associated with normal ageing, but defective repair in brain cells can contribute to neurological dysfunction directly and indirectly (Barzilai, 2013). The DNA damage response (DDR) may have particular relevance for neuronal development and the onset and progression of many neurodegenerative diseases associated with an increase in oxidative stress including AD (Barzilai et al., 2008; Bohr, 2008). For instance, subtle variation in base excision repair (BER) capacity has been assessed, showing that polymorphism in BER genes may play a role in ageing-related cognitive performance and decline (Lillenes et al., 2011). Furthermore, in an AD mouse model, differences in transcriptional expression of BER genes OGG1, APE1 and Polβ in brain tissues between AD and wildtype mice have been demonstrated (Lillenes et al., 2013). Thus, BER gene expression patterns in AD mice reflect DNA repair responses to oxidative stress with age.

Inflammation is another potential driver of neurodegeneration, ageing and life-span in evolution (Finch, 2010). Astrocytes play a predominant role in the cellular response to meningitis and other microbial infections (Davidson et al., 2007), events which might accelerate inflammation and brain ageing. On the other hand, astrocytes can respond to TNF-α induced inflammation by releasing BDNF, which has neuroprotective properties (Saha et al., 2006). In this respect, it is interesting that polymorphisms in DNA repair genes may influence expression of APP and secretases including presenilin, possibly contributing to mild cognitive impairment (MCI) and AD (Marambaud et al., 2003). Thus, it would be interesting to explore whether and how microbial components, exosomes and inflammation influence membrane ultrastructure and trigger astrocyte-specific Aβ fibril processing in normal brain ageing, CNS infections and AD (Davidson et al., 2007). Genetic predisposition/DNA repair competency (possibly linked to specific and consequent SNP profile) may also influence the structure and function of membrane proteins; this could predispose for astro- and neurodegeneration (Bishop et al., 2010; Bohr, 2008).

3. Brain structure, function and disease

3.1. Brain volume, water and ion homeostasis

Astrocytes are connected by gap junctions and form a functional syncytium (Lee et al., 1994). Changes in the intracellular or extracellular volume can have dramatic effects on brain function, in part because the extracellular volume is a determinant of the concentration of ions and other solutes in the interstitial fluid. When astrocytes swell in response to hypoxic stress, they release K⁺, Cl⁻, organic osmolytes, and water to restore their volume. This process is called regulatory volume decrease (RVD) and is associated with a rise in intracellular [Ca²⁺] (Pasantes-Morales et al., 2006). Some of the released solutes (glutamate, taurine, ATP) may regulate the activity of neurons, glial cells and the vasculature, and may perform roles in specific signalling pathways. Although it is clear that intracellular and extracellular volume are tightly regulated in the brain, the mechanisms involved in this process are poorly understood (Benfenati et al., 2011; Thrane et al., 2011).

The BBB mediates selective transport of substances between the blood and the brain. Loss of BBB integrity is implicated in neurodegenerative diseases, including stroke and dementia (Palmer, 2011). We recently provided evidence that astrocytes play a role in maintaining BBB integrity (Amiry-Moghadam et al., 2004; Haj-Yasein et al., 2011). AQP4-enriched foot processes ensheath brain microvessels, such that astrocytes are the initial sites of water entry during brain edema formation (Nase et al., 2008). Moreover, brain edema is eliminated by AQP4-dependent-mechanisms, probably also involving astrocyte processes bordering the subarachnoid space and the ventricles (glia limitans externa and glia limitans interna, respectively) (Papadopoulos et al., 2004). Thus, astrocytes play a key role in preventing volume perturbation in the brain (Benfenati et al., 2011).

AQP4 may act as a sensor of vascular tone and promote release of effector molecules that promote neurovascular coupling. It is well known that ECV varies during normal synaptic activity, as well as with life stage and with certain neurological diseases. Recent research suggests that AQP4 regulates ECV and the resorption of interstitial fluid (Haj-Yasein et al., 2011, 2012). Notably, AQP4 also facilitates clearance of interstitial solutes, including Aβ, and promotes recycling of CSF from the subarachnoid space into the brain parenchyma along paravascular spaces of penetrating arteries (Iliff et al., 2012). The latter breakthrough discovery was made by imaging extracellular fluorescent tracers in living mice with two-photon microscopy. Thus, it was shown that AQP4 controls the composition and turnover of the fluid that surrounds neurons. A failure of astrocytes and aquaporins to promote circulation of interstitial fluid may cause misfolded proteins to accumulate in brains of individuals with AD or other neurological diseases. In support of this hypothesis, AQP4 expression is altered in an animal model of AD (Yang et al., 2011). The precise mechanisms by which AQP4 regulates circulation of the interstitial fluid and promotes Aβ clearance are poorly understood.

3.2. Sculpting the action potential: the Na⁺/K⁺ATPase

Several neurological syndromes have been linked to defective P-type ATPases, including familial hemiplegic migraine (sodium pump α2) (De Fusco et al., 2003; Morth et al., 2009) and rapid-onset dystonia parkinsonism (sodium pump α3) (de Carvalho Aguiar et al., 2004), while AD has mainly been linked to a specific flipase from the P4-ATPase sub-group (Folmer et al., 2009). However, specific treatment of astrocytes with the Aβ 25–35 peptide increases intracellular sodium and potassium and is associated with reduced levels of sodium pump and the
sodium-dependent glutamate transporters, GLAST and GLT-1 (Vitvitsky et al., 2012).

3.3. Changes in white and gray matter with ageing

Age-related changes in gray and white matter across the human lifespan have recently been mapped using Magnetic Resonance Imaging (MRI) and from Diffusion Tensor Imaging (DTI) (Fig. 2). Data were analysed to determine cortical thickness, subcortical volume, and microstructural properties. The results identify changes that may relate to risk for MCI and AD (Fjell et al., 2009a,c, 2010a,b; Walhovd et al., 2009, 2010a,b). Although neurobiological mechanisms remain to be established, MRI studies may help identify glia-related changes in human development, plasticity and ageing. While white matter changes are obvious candidate indicators of glia-related change, changes in gray matter compartments may also play a role, as they have been correlated with astrocyte activation (Blumenfeld-Katzir et al., 2011).

The process of myelination critically depends on glia, namely the proliferation, development and integrity of oligodendrocytes. The amount of both gray and white matter increases sharply in the first few years of life. Thereafter, gray matter volume, including cortical thickness, steadily decreases, while white matter volume continues to increase well into adulthood and later life (Fjell et al., 2009b; Østby et al., 2009; Tammes et al., 2010; Walhovd et al., 2005, 2011). Cortical thinning during development likely reflects synapse pruning, where synapse elimination refines connectivity and enhances efficiency of signal transmission and cognition, as well as progressive proliferation of myelin into the neuropil. However, in older individuals, cortical thinning may reflect degenerative processes linked to cognitive decline, such as neuronal shrinkage, deafferentation and reduction in synaptic density. Although cortical thickness decreases from childhood to old age, this decrease is not typically detected in anatomical MRI scans; thus, maturational and degenerative processes cannot readily be distinguished by MRI alone. However, $T_1$-weighted signal intensity can differentiate cortical maturational and ageing-related processes (Westlye et al., 2010). Therefore, multimodal approaches may be needed to detect and understand white and gray matter dynamics at the cortical boundary.

Human cognitive training-induced changes have been observed by MRI in white and gray matter. Myelination can occur in an activity-dependent manner (Fields, 2005) and accumulating evidence suggests that astrocytes are involved in learning and memory. Notably, recent studies show that episodic memory and spatial learning correlates with region-specific changes detectable by DTI, including increased fractional anisotropy and decreased mean diffusivity (Blumenfeld-Katzir et al., 2011; Engvig et al., 2012a; Sagi et al., 2012), and comparison of MRI with histological findings suggest that astrocytes do play a role in mediating these changes (Blumenfeld-Katzir et al., 2011; Johansen-Berg et al., 2012). Specifically, in parallel human and animal models of neuroplasticity, MRI and histological analysis of rat brains indicate that in regions of MD decrease following learning (water maze task), there is an increase in number of synaptic vesicles, astrocyte activation and astrocytic processes, as well as increase in BDNF (Sagi et al., 2012). However, the relationship between changes in MRI water signals and plastic phenomena at the cellular level is still unclear and insufficiently studied. Therefore, additional studies are needed to determine whether and how astrocyte plasticity influences age-related cognitive change. In this context novel diffusion MR technologies, such as e.g. restriction spectrum imaging (RSI) may offer new possibilities for in vivo monitoring of subtle structural changes in the brain by selective measurement of microscopic-scale water displacement in different cellular compartments (White et al., 2013). Astrocyte plasticity may play critical roles during repetitive cognitive training (spatial memory, object recognition, visual discrimination and memory training) in both humans and animal models. Such plasticity related changes can be analysed in young and old animals by use of combined multi-modal methodologies (Fig. 3), measuring structural and functional tissue parameters, such as in vivo two-photon imaging (Fig. 1C) and RSI (White et al., 2013) in combination with ex vivo histological methods including immunofluorescence (Fig. 3E and F; Thrane et al., 2011) and conventional histology (Fig. 3G). Novel digital brain atlasing tools (Hjornevik et al., 2007; Papp et al., 2013) facilitate assignment of anatomical location and provide the spatial reference framework needed to integrate the results from multimodal investigations (Fig. 3).

4. Connecting molecular events to cognition

4.1. Leveraging biomolecular tools to understand the human brain

Neuropsychology, human brain imaging, optogenetics, microbiology, nanobiology, neuroinformatics, and structural biology are convergent approaches that are well suited to answer urgent questions about how astrocytes contribute to brain function and dysfunction. If applied and developed to characterize brain (dys) function in individual patients, this approach will facilitate early disease detection and treatment, and lead to improved individual healthcare. Human clinical materials (astrocyte cell...
cultures from mice and humans, mice models as well as human biobank materials), genome-wide association studies (GWAS/SNP analysis), gene expression (mRNA), microRNA (miRNA), metabonomics and CSF proteomics profiles should be examined in astrocytes from normal or diseased human brains, while human patients and normal controls should be subjected to neuropsychological testing and refined neuroanatomical/microstructural measures (MRI).

4.2. Astrocyte-neuron communication in the intact brain

Gliotransmitters play highly specific roles in communication between astrocytes and neurons. Previous studies on astrocyte-neuron signalling have used patch clamp electrophysiology in brain slices in vitro. Novel approaches employ two-photon imaging and localized photolysis of caged compounds, stimulating release of gliotransmitters from astrocytes by uncaging Ca\(^{2+}\) ions, and providing information on Ca\(^{2+}\) flux and membrane depolarisation in neurons (Fig. 1C). Inhibitors of specific gliotransmitter receptors enable the identification of molecular components of the signalling pathway. Proteins that control gliotransmitter release are known and can be selectively inhibited with siRNAs/miRNAs. Optogenetic tools developed to enhance the efficiency of such experiments and to specifically stimulate (or inhibit) gliotransmitter release from astrocytes can be used in combination with high-resolution two-photon live imaging and 3D EM (Bourne and Harris, 2011). A comprehensive description of the role of gliotransmitters in synaptic transmission is also found in reviews by De Pitta and co-workers (De Pitta et al., 2011, 2012).

4.3. Role of astrocyte plasticity in age-related cognitive decline

Our hypothesis is that if astrocyte plasticity is critical for cognitive function in animals (Fig. 3), the same is true in humans (Johansen-Berg et al., 2012; Sagi et al., 2012). We have shown that cognitive training can improve cognitive function, and that training is accompanied by macro- and microstructural changes in brain gray and white matter detectable by MRI (Engvig et al., 2010, 2012a; Engvig et al., 2012b) (Fig. 2). We presume that the changes are functionally significant, because they appear to be linearly related to the amount of cognitive behavioral gain. Nevertheless, the exact mechanism and temporal relationships are unknown. Future studies to address unanswered questions could include water diffusion MRI and RSI/PDD and studies of cognition in normal human subjects before and after intensive cognitive training. The goal is to delineate the molecular changes underlying cognitive gains in human ageing.

4.4. Cerebrovascular regulation and CNS infection in ageing and AD

AD is associated with altered molecular organization of astrocytic endfeet, which is characterized as a form of astrodegeneration. Cerebro-vascular function in the brain is tightly regulated by astrocytes (Gordon et al., 2007; Iadecola and Nedergaard, 2007), and the relationship between astrodegeneration and vasoregulation in the brains of mice with or without AD-like pathology should be examined. Another related goal is to define and differentiate valid biomarkers for AD and cerebrovascular dementia.

Astrocytic processes are located at the interface between brain neuropil and liquor spaces (blood and CSF). Therefore, astrocytic processes are among the first compartments to be exposed to microbes, inflammatory mediators and environmental toxins, when they enter the brain. However, how astrocytes respond to such stimuli is poorly understood. Responses to microbes/microbial components are critical during periods of exposure to meningitis-inducing agents (Davidsen et al., 2007), which can be retrogradely transported from the nasal mucosa through polarised astrocytes and/or neurons to the CNS. During such exposures, astrocytes could act as drivers of ageing, meningitis and AD, more so in genetically-predisposed individuals (Fig. 4). Cognitive testing and clinical studies are appropriate using exposed human patients with and without cognitive decline.
5. Prospects for interventions

5.1. The link between physical activity and preserved brain function during ageing

Physical exercise augments brain function in old age, and is thought to protect against cerebrovascular disease, MCI and AD (Foster et al., 2011). Exercise is a low-cost, low-risk measure; its precise mechanisms of action are not known, but may involve astrocytes (Latimer et al., 2011). A recently identified putative mediator is erythropoietin (Epo), an important neurotrophic and neuroprotective agent in brain that enhances recovery of lost memory function after cerebral ischemia (Unden et al., 2013). Epo enhances exercise performance, without affecting erythropoiesis (Schuler et al., 2012), suggesting the possibility that exercise might increase the level of Epo in the brain. Epo also increases in the brain after antidepressive electroconvulsive treatment, and administration of Epo alleviates depression and improves cognition; it also induces the expression of genes encoding neurotrophic factors such as brain derived neurotrophic factor (BDNF) (Girgenti et al., 2009), which is central to the effects of physical exercise on the brain.

Numerous studies indicate that BDNF mediates beneficial effects of physical exercise on learning/memory and problem solving. BDNF also mediates changes in cortical volume, neurogenesis and synaptogenesis, and may mitigate functional loss associated with AD, other forms of dementia, Parkinson’s disease and depression (Adlard et al., 2011; Berchtold et al., 2010; Erickson et al., 2011; Foster et al., 2011; Nagamatsu et al., 2013; Zschucke et al., 2013). Low BDNF in brain and in blood is associated with cognitive impairment and AD (Komulainen et al., 2008; Laske et al., 2006). Brain neurons appear to be the major source as well as the major site of action of BDNF, indicating that it is a neuro-autocrine factor. Most if not all brain neurons produce BDNF, which is released from brain to blood, and the release is increased by physical exercise (Rasmussen et al., 2009; Seifert et al., 2010). Exercise causes the level of BDNF in brain and blood to increase by an unknown mechanism. Lactate may stimulate production of BDNF by astrocytes and other neuronal cells (Coco et al., 2013). Interestingly, the effect of lactate on BDNF was lost after long term exposure in neuronal but not in astroglial cells and multiple reports implicate cAMP response element binding protein (CREB) and cAMP (Kida, 2012). The G-protein coupled lactate receptor GPR81 (HCA1), which controls lipolysis in adipose tissue, was recently discovered in brain and shown to downregulate cAMP levels (Lauritzen et al., 2013), in agreement with the proposed “volume transmitter” role of lactate (Bergeresen and Gjedde, 2012) and suggesting that the lactate receptor may regulate BDNF
function. Potentially, Epo (see above) also takes part in this regulatory network. The involvement of multiple interacting signalling routes with different time dependence invites the suggestion that the intermittent nature of exercise induced lactate level increase may be important for the final effect. It may be conducive to inducing preconditioning mechanisms involving astrocytes (McKenzie et al., 2012), which are protective against several forms of brain injury, and offers a possible basis for the well known efficacy of high intensity interval training on muscular and cardiovascular function (Wisloff et al., 2007), which remains to be evaluated on brain function.

Telomere length is inversely related to ageing, and several reports indicate that telomere shortening is counteracted by physical exercise (LaRocca et al., 2010; Osthus et al., 2012). In mitotic cells, chromosome ends (telomeres) are maintained during successive cell divisions by telomerase, a reverse transcriptase. The exercise-enhanced maintenance of telomere length may be related to enhanced BDNF activity: BDNF increases neuronal expression of telomerase, which mediates an augmented resistance to apoptosis (Fu et al., 2002; Niu and Yip, 2011). Interestingly, conditioned medium from astrocytes overexpressing telomerase is reported to protect neurons from hypoxic–ischemic damage (Duan et al., 2010). In vivo, hypoxia–ischemia upregulates telomerase in neurons and astrocytes, which inhibits neuronal apoptosis and curbs reactive gliosis (Qu et al., 2011), suggesting telomerase as a target for neuroprotective intervention.

5.2. Discovery-based approach to understanding brain ageing and disease

Advanced data management and data integration will be required in order to study complex problems as outlined in the present review (Fig. 3). Studies of glial cells range from the molecular and cellular levels to whole brain and behavioral analysis. Data on glial cells collected at one level of investigation will have to be integrated with other glial cell data at all scales of investigation. Further, in order to ultimately enhance our understanding of brain ageing and brain disease, glial cell data will have to be analysed in the context of other data categories, related to other cell types and relevant structure–function relationships. Coordinated efforts in the field of data management and integration, with focus on data sharing, analytical tools, and modelling and simulation, have been introduced recently and will facilitate progress in the field of brain ageing and disease (Akil et al., 2011; Bjalia, 2008). A systematic approach to data integration implies: (1) management and analyses of heterogeneous data types and structured metadata; (2) dissemination and sharing of data through online data repositories with relevant levels of access for collaborating laboratories and the larger scientific community, and (3) federation of data repositories through internationally coordinated services. Examples of recent progress in these areas include the services provided by the International Neuroinformatics Coordinating Facility and the Neuroscience Information Framework (Akil et al., 2011; Bjalia and Grillner, 2007; Hamilton et al., 2012) and more specialized initiatives providing access to large scale data sets for research on brain diseases, e.g. The Alzheimer’s disease neuroimaging initiative (Weiner et al., 2010).

6. Conclusions

The “glia doctrine” and “healthy brain approach” are timely concepts because populations worldwide face the challenge of a rapidly ageing human society with an increasing fraction of non-working elderly. Dementia and other ageing-related diseases cause much personal suffering and their management consumes a disproportionate fraction of socioeconomic and healthcare resources. Therefore, it is essential that we take action now and aggressively pursue research that will help minimise this burden and reduce the costs associated with age-related brain disease.

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