Environmental Toxicology and Pharmacology 84 (2021) 103608

Contents lists available at ScienceDirect

Environmental Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/etap

Review

Environmental toxicants in the brain: A review of astrocytic metabolic dysfunction

Mondona S. McCann [a,*], Kathleen A. Maguire-Zeiss [a,b]

[a] Interdisciplinary Program in Neuroscience, Georgetown University Medical Center, Washington, DC, 20057, United States
[b] Department of Neuroscience, Georgetown University Medical Center, Washington, DC, 20057, United States

ARTICLE INFO

Edited by Dr. M.D. Coleman

Keywords:
Glia
Organochlorines
Polychlorinated biphenyls
Dioxin
Manganese
Glutathione
Glucose
Metabolism
Neurodegeneration

ABSTRACT

Exposure to environmental toxicants is linked to long-term adverse outcomes in the brain and involves the dysfunction of glial and neuronal cells. Astrocytes, the most numerous cell type, are increasingly implicated in the pathogenesis of many diseases of the central nervous system, including neurodegenerative diseases. Astrocytes are critical for proper brain function in part due to their robust antioxidant and unique metabolic capabilities. Additionally, astrocytes are positioned both at the blood-brain barrier, where they are the primary responders to xenobiotic penetrance of the CNS, and at synapses where they are in close contact with neurons and synaptic machinery. While exposure to several classes of environmental toxicants, including chlorinated and fluorinated compounds, and trace metals, have been implicated in neurodegenerative diseases, their impact on astrocytes represents an important and growing field of research. Here, we review existing literature focused on the impact of a range of synthetic compounds on astrocytic function. We focus specifically on perturbed metabolic processes in response to these compounds and consider how perturbation of these pathways impacts disease pathogenesis.

1. Introduction

It is increasingly appreciated that astrocytes play an important role in the pathophysiology of central nervous system (CNS) disorders and diseases, ranging from developmental to neurodegenerative (Liddelow and Barres, 2017). Through their homeostatic, antioxidant, and metabolic functions, astrocytes are critical for the maintenance of lifelong brain health. The etiology of many neurodegenerative diseases is understood to be multifactorial, involving a deleterious confluence of genetic and environmental influences (Bossy-Wetzel et al., 2004; Fleming, 2017). Several classes of environmental toxicants are known to have widespread, damaging effects on CNS health and function (Cannon and Greenamyre, 2011).

Importantly, the response of astrocytes to environmental toxicants is crucial to understanding the impact on the whole brain, as perturbation of astrocytic function has far-reaching consequences. This is partly due to the relative abundance of astrocytes compared to other brain cells (Han et al., 2013) and their proximity both to synapses (Agulhon et al., 2008; Allen and Eroglu, 2017) and the blood-brain barrier (Kacem et al., 1998) where they comprise the first line of defense against xenobiotic penetrance of the CNS (Dringen and Hirrlinger, 2003). Importantly, in addition to their cytoarchitectural and morphological characteristics, the unique biochemical (reviewed in (Souza et al., 2019)), antioxidant (Dringen and Hirrlinger, 2003) and metabolic profile (Bélanger et al.,

Abbreviations: AD, Alzheimer's disease; AHR, aryl hydrocarbon receptor; ARE, antioxidant response element; CNS, central nervous system; CYP, cytochrome P450; EAAT1, excitatory amino acid transporter-1; ECs, endothelial cells; EETs, epoxyeicosatrienoic acid; GCL, glutamate cysteine ligase; GFAP, glia fibrillary acid protein; GLAST, glutamate aspartate transporter; GLUT1, glucose transporter-1; GPX, glutathione peroxidase; GSH, reduced glutathione; GSS, glutathione synthetase; GSSG, oxidized glutathione; H_2O_2, hydrogen peroxide; HO1, heme-oxygenase-1; IL-1β, interleukin 1 beta; IP_3R, inositol-trisphosphate receptors; KEAP1, kelch-like erythroid cell-derived protein; MRP, multidrug resistant protein; NADPH, nicotinamide adenine dinucleotide phosphate; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; NQO1, NAD(P)H quinone dehydrogenase-1; NRF2, nuclear factor erythroid 2-related factor 2; MAPK, mitogen-activated protein kinase; PCB, polychlorinated biphenyl; PD, Parkinson's disease; PFA, per/poly fluoroalkyl; PFC, perfluorinated compound; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; PGE_2, prostaglandin E2; POP, persistent organic pollutant; ROS, reactive oxygen species; S100B, S100 calcium binding protein B; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; TNFα, tumor necrosis factor-α; γGluCys, γ-glutamylcysteine.

* Corresponding author.
E-mail address: msm302@georgetown.edu (M.S. McCann).

https://doi.org/10.1016/j.etap.2021.103608
Received 19 October 2020; Received in revised form 24 January 2021; Accepted 29 January 2021
Available online 5 February 2021

2011; Brown and Ransom, 2007) of astrocytes, some of which are outlined in this review, enables these cells to respond robustly and effectively to xenobiotics in the CNS. Furthermore, evidence from primary murine cell culture suggests that the antioxidant reserves of astrocytes are maintained into senescence (Liddell et al., 2010).

While the specific impacts of many toxicants on astrocytes have not been well-studied, as our scientific view of the CNS expands to further appreciate the critical role of glial cells in preserving proper functioning, there is growth in this area of research. In particular, research on environmental toxicants within the CNS is incomplete without an understanding of how astrocytic metabolic dysfunction, as a result of both acute and chronic exposure to toxicants, contributes to the breakdown of homeostasis and attendant neural degeneration. Specifically, as the metabolism of astrocytes is so important for brain health, disruption of astrocytic metabolic processes by environmental toxicants is an important, emerging area for understanding neurologic diseases wrought, either in part or in totality, by exposure to these toxicants.

There is an indissociable link between astrocyte metabolism and neuronal function through several pathways including the glutamate-glutamine cycle, glutathione synthesis, and the lactate shuttle (Bélanger et al., 2011). Due to several astrocyte-specific characteristics, including antioxidant capacity, expression and activity of xenobiotic and metabolism-related enzymes, and cellular location within the parenchyma, these cells are uniquely situated to respond to the toxicants discussed herein. Furthermore, the astrocytic response to toxicants can trigger a secondary insult to neurons whereby converging factors, such as a deficit in physiologic support and/or the release of toxic factors (directly or through recruitment of other cell types) exacerbates the primary effects of toxicants. As such, our understanding of the CNS' response to and recovery from environmental toxicant exposure must include the cellular, metabolic and functional outcomes of astrocytic processes.

Humans are exposed to multifarious toxicants through our natural and built environments. As age is the primary risk factor for neurodegeneration, researchers have long queried the impact of chronic exposure to toxicants and the ability of these toxicants to cause or contribute to neurodegeneration, such as in the context of Alzheimer's (AD) or Parkinson's disease (PD). This exposure includes toxicants that are intentionally produced to be toxic to another species, such as herbicides and insecticides, compounds with unintended toxic effects, byproducts of synthetic reactions with toxic effects, and biologically relevant metals that are toxic at elevated levels.

As glial-centered toxicology research increases, focusing on astrocytic physiological functions, specifically metabolic processes that are understood to be critical for homeostasis (Weber and Barros, 2015), and subsequent dysfunction wrought by exposure to toxicants is critical to understanding the response of the CNS to xenobiotic compounds (Fig. 1). Here, we consider the properties of synaptic and perivascular astrocytes and the machinery underlying astrocytic metabolic and antioxidant functions. We then review the astrocyte-focused literature regarding a subset of toxicants united by the shared characteristic of association with neurodegeneration. Finally, we evaluate the importance of astrocytic metabolism in the response to xenobiotic compounds.

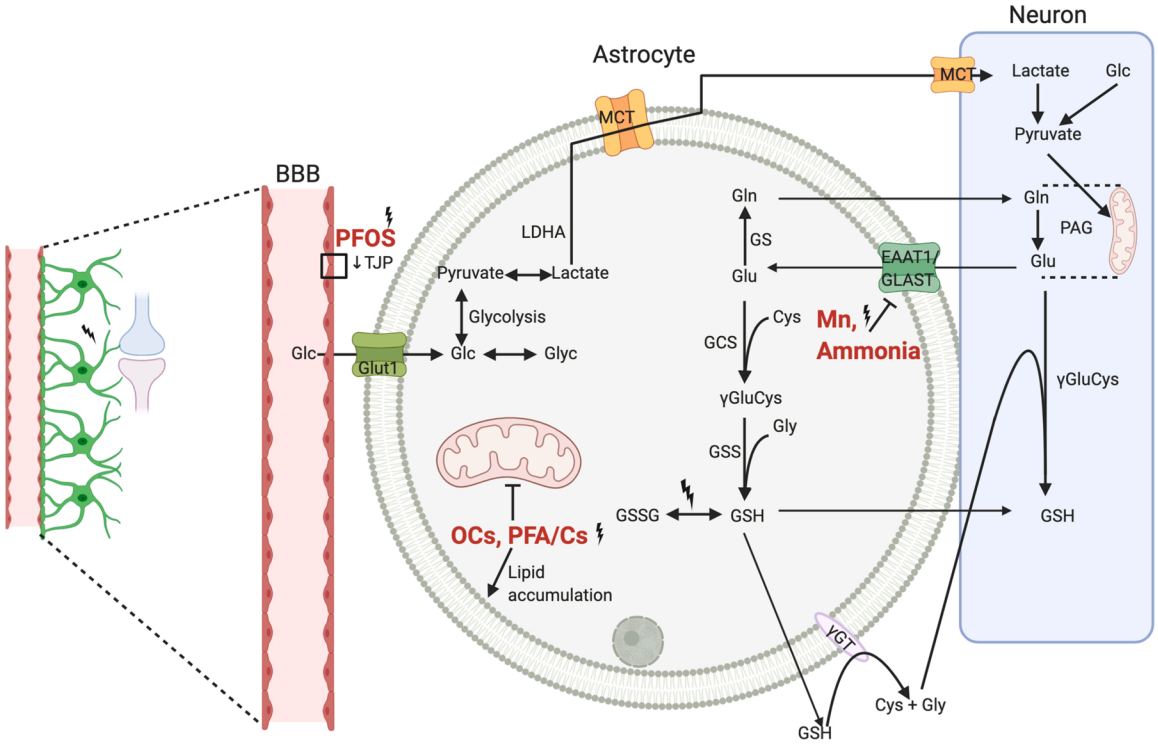

Fig. 1. The multifunctional role of astrocytes in brain homeostasis. Schematic illustrating metabolic interactions between astrocytes (green), blood vessels (red) and neurons (blue) and the impact of certain environmental toxicants (ammonia, Mn, OCs, PFOS, PFAs, PFCs). Astrocytic endfeet ensheathing the vasculature uptake glucose (Glc) from blood vessels through the GLUT1 transporter. Glucose is utilized as a substrate for glycolysis, resulting in the production of pyruvate, or stored as glycogen (Glyc). Some of this pyruvate is converted into lactate by lactate dehydrogenase, an oxidoreductase, which is released into the extracellular matrix via monocarboxylate (MCT) transporters and taken up by neurons through the same transporters. Glutamate (Glu) is released from pre-synaptic neurons during neurotransmission into the synaptic cleft, where excess glutamate is taken up by perisynaptic astrocytic processes (PAPs) via Na^{+}-dependent excitatory amino acid transporters (EAATs). In astrocytes, Glu is converted to glutamine (Gln) by glutamine synthetase (GS). Gln is utilized by phosphate-activated glutaminase (PAG) in neurons to synthesize Glu, which is then put into vesicles for synaptic release. Glutamate is also converted to α-ketoglutarate by glutamate dehydrogenase or aspartate aminotransferase for metabolism in the TCA cycle (not pictured). Finally, Glu is converted to glutathione (GSH) through two consecutive ATP-consuming reactions, involving the ligation of Glu and cysteine by γ-glutamylcysteine synthetase (GCS) to form γ-CysGly, which is subsequently converted to GSH by glutathione synthetase (GSS). Astrocytes release GSH which cleaved by ectoenzymes to form CysGly, the precursor for neuronal GSH synthesis.

2. Synaptic astrocytes

Astrocytes have disparate functions and morphology both throughout development and in different anatomical regions of the adult brain. While it is clear that heterogeneity exists in astrocytic properties across developmental trajectory and anatomical region, evidence suggests that, throughout the brain astrocytes maintain homeostasis through several antioxidant functions and metabolic processes (Bélanger et al., 2011; Chai et al., 2017). Astrocytic lineage is from the ectoderm and, once mature and fully branched, these complex cells can form connections with approximately 2 million synapses (Han et al., 2013). In all brains, regardless of health, injury or age, astrocytes monitor the microenvironment and work toward homeostasis by promoting neuronal health and function through several unique functions (Verkhratsky et al., 2019). Astrocytes *in vivo* are coupled in syncytia, enabling these cells to rapidly transmit information across large distances through gap junctions. Populations of protoplasmic astrocytes form functional regions with the gray matter, where astrocytes in a syncytium form "tiles" that serve to segregate neurons and constitute a functional parcellation of brain regions (Halassa et al., 2007).

The "tripartite synapse" (Araque et al., 1999) is comprised of pre- and post-synaptic neurons in close contact with synaptic astrocytes, supporting the idea that astrocyte location facilitates these unique macroglial functions. The linkage of the perisynaptic astrocytic "tip" processes that ensheathe synapses is dynamically regulated in an activity-dependent manner (Bernardinelli et al., 2014), such that not all synapses are encapsulated by astrocytes invariably throughout development and maturation. Perisynaptic astrocytes express several classes of transporters and receptors that function in the service of proper neurotransmission, clearance, and ionic homeostasis (Olsen et al., 2015). These include: metabotropic and ionotropic glutamate receptors, potassium transporters (Djukic et al., 2007), and glutamate transporters (Murphy-Royal et al., 2020), which are enriched on the astrocytic processes contacting synapses. Following neuronal firing and the release of neurotransmitters, perisynaptic astrocytes release stores of intracellular calcium as a result of metabotropic neurotransmitter receptor activation, upstream of inositol 1,4,5-triphosphate receptor activation (IP_3R) signaling (Bazargani and Attwell, 2016; Otsu et al., 2015). This intracellular calcium release is thought to trigger astrocytic glutamate release which can affect neighboring cells (Parpura et al., 1994), as well as the insertion of glucose transporters into the membrane to increase glucose availability in response to neuronal demand (Loaiza et al., 2003; Pellerin and Magistretti, 1994). Increased intracellular calcium precipitates the release of several glial factors (including ATP,D-serine, and glutamate); this bidirectional interplay positions astrocytes in a synapto-modulatory role (Papouin et al., 2017).

One example of this modulation in the form of metabolic coupling is the glutamate-glutamine cycle, in which astrocytes utilize glutamate transporters to uptake this synaptic neurotransmitter then convert glutamate into glutamine which is released for neuronal glutamate synthesis (Tani et al., 2014). The lactate shuttle is another example of this coupling as indispensable machinery (Pellerin et al., 1998). Briefly, the lactate shuttle occurs when glutamate released by neurons during synaptic activity is taken up by astrocytes and stimulates the production of lactate from glucose. Astrocytic lactate is then released and taken up by nearby neurons wherein it is used to produce ATP, further fueling synaptic activity and closing the metabolic loop between glycolytic astrocytes and oxidative neurons (Fig. 1).

The coordination of astrocytic populations across synaptic boundaries permits rapid information transfer and concurrent processes within the astrocytic syncytia, which can be in contact with an estimated 600 dendrites and 100,000 synapses (Halassa et al., 2007). The metabolic processes, including the glutamate-glutamine cycle and lactate shuttle, triggered by synaptic transmission are examples of how neuronal function is linked to astrocytic metabolism (Bélanger et al., 2011). Moreover, this rapid system of information transfer is hypothesized to connect synaptic astrocytes with those at the blood-brain barrier as astrocytic intracellular calcium increases form the mechanistic basis for functional hyperemia, wherein neural activity is accompanied by increased blood flow (Gordon et al., 2007; Tran et al., 2018).

3. Perivascular astrocytes

Partially due to their position at the blood-brain barrier (BBB) and at synapses, astrocytes are uniquely situated to link neuronal firing to the vasculature. The brain capillary endothelial cells (ECs) forming the BBB are comprised of tight junctions that regulate the passage of peripheral solutes into the CNS. Here, astrocytic endfeet abutting the vasculature work in concert with other cell types (including neurons and pericytes, in addition to ECs) to form the neurovascular unit and regulate CNS access as part of this homeostatic interface (Harder et al., 2002; Hawkins and Davis, 2005; Iadecola, 2017). This positioning allows astrocytes to coordinate neuronal signaling with blood flow, as the short distance (8−20 μm) (Schlageter et al., 1999) between neurons and capillary-forming ECs is traversed by astrocytic endfeet. In this way, a bidirectional system is formed whereby the astrocytic response to neuronal activity results in vasodilation and increases in cerebral blood flow. The mechanism for this vasodilation is theorized to be through release of metabolites of arachidonic acid (including epoxyeicosatrienoic acids [EETs] and prostaglandin E2 [PGE_2] via the cyclooxygenase and cytochrome p450 pathways, respectively) (Attwell et al., 2010; Zonta et al., 2003). Through this coupling, astrocytes play an important role in both the formation, maintenance and repair of the BBB as well as the coordination of neuronal signaling and cerebral flood flow (Abbott et al., 2006).

Importantly, perivascular astrocytic endfeet express the transmembrane water channel, Aquaporin-4 (AQP4), which is organized into orthogonal array of particles (OAPs) and anchored to the endfoot in an agrin-dependent manner. AQP4 plays an important role in CNS water homeostasis and its function is critical both during normal and recovery processes, such as during edema (Amiry-Moghaddam and Ottersen, 2003). Through its water transport function, AQP4 is linked to glutamate reuptake as the astrocytic sodium-dependent glutamate transporters (GLTs; EAATs) necessitate the coupling of glutamate to both sodium and water molecules (MacAulay et al., 2004). Furthermore, there is down-regulation of glutamate transporter-1 (GLT-1) in AQP4-knockout mice concurrent with decreased cellular glutamate toxicity (Zeng et al., 2007).

Both glial and BBB dysfunction are associated with myriad diseases and disorders including: stroke, traumatic brain injury, multiple sclerosis, epilepsy, Parkinson's and Alzheimer's disease (reviewed in (Burda et al., 2016; Pekny et al., 2014; Rodríguez-Arellano et al., 2016)). As perivascular astrocytes are critical for a functioning BBB, in part due to their role in the neurovascular unit and their expression of AQP4, understanding the role of astrocytic dysfunction in the pathology of neurodegenerative diseases is essential for advancement. Importantly, AQP4 is a major component of the glymphatic clearance pathway which, like the eponymous lymphatic system, removes waste from the CNS. There is evidence that this clearance consists of bulk flow (a result of arterial pulsations) that drives CSF-ISF exchange and ultimately results in drainage of waste products in the perivascular space (Abbott et al., 2018; Rasmussen et al., 2018). With respect to neurodegenerative diseases that involve protein aggregates (such as Alzheimer's and Parkinson's disease), it is hypothesized that this glymphatic clearance is impaired with aging and that this impairment contributes to aberrant protein accumulation (Iliff et al., 2013, 2012; Rasmussen et al., 2018).

4. Astrocytic metabolism

4.1. Glucose

The CNS primarily relies on glucose for energy and consumes

approximately 20% of the body's glucose, despite being merely 2% of the body's mass. The reliance of the CNS on oxidizing glucose for energy contributes to the brain's comparatively high vulnerability to oxidative stress. Glucose in the CNS is metabolized through the same pathways as other organ systems including tricarboxylic acid cycle (TCA) activity, glycolysis, and the pentose phosphate pathway, as well as glycogenesis, which is specific to astrocytes in the CNS (Fig. 1). The many metabolic intermediates (including lactate and glutamate) formed by these processes serve as energy reserves too. Importantly, CNS glucose functions as the biosynthetic precursor for several neurotransmitters, like glutamate and γ-aminobutyric acid (GABA), as well as molecules like aspartate and glutathione that are involved in many cellular processes (Bélanger et al., 2011). When glutamate, the main excitatory neurotransmitter, is released from neurons glycolysis is triggered in nearby astrocytes (Pellerin and Magistretti, 1994), providing further evidence for the bidirectional metabolic coupling between neural activity and astrocytic glucose utilization.

The disparity between the concentration of CNS capillary blood glucose, approximately 3−6 mM, and the concentration of glucose in the parenchyma, 0.5−1 mM (Dienel, 2019) suggests that the astrocytic processes wrapping around the vasculature are important for glucose uptake and entry into the parenchyma, specifically through the glucose transporter-1 (GLUT1) (Loaiza et al., 2003). This finding supports the idea that the cytoarchitectural proximity of astrocytes to neurons is critical for neuronal support as, even though astrocytes require much less glucose than neurons to support their physiological function, they are positioned to be the first receivers of this energetic substrate (Bélanger et al., 2011). The GLUT1 transporter represents a mechanism by which astrocytes respond to metabolic stress and meet the demands of glutamate clearance in the astrocyte-neuron metabolic interface (Loaiza et al., 2003).

Importantly, metabolic diseases like diabetes mellitus and metabolic syndrome that involve dysregulation of glucose systems are increasingly associated with environmental toxicant exposure (Sargis, 2014). In astrocytes, glucose utilization is closely linked to neuronal signaling (Bélanger et al., 2011). GLUT1 is the only isoform expressed by cortical astrocytes; the activation of astrocytic glycolysis by the release of neuronal glutamate necessitates GLUT1-transported glucose (Loaiza et al., 2003). Stimulation of GLUT1 can be modulated by metabolic stress in some cells (Barnes et al., 2002), as well as cytosolic calcium concentrations (Quintanilla et al., 2000), suggesting this pathway as a mechanism for toxicant-induced astrocytic dysfunction.

4.2. Glycogen

While neurons express the enzymes necessary to metabolize glycogen, neuronal glycogen storage is only seen under pathological conditions. Glycogen in the brain is predominantly found in astrocytes and approximately 40% of CNS glucose is metabolized into glycogen by these cells (Brown and Ransom, 2007). The inability of neurons to store glycogen leaves astrocytes as the primary supplier of glycogen-derived lactate and pyruvate during periods of exceptionally high metabolic demand (Brown and Ransom, 2014), such as memory formation (Gibbs et al., 2006).

The metabolism of glycogen, a short-term reserve for glucose production, is also important for astrocytic potassium and glutamate uptake. Astrocytes increase their glycolytic capacity in response to certain forms of injury, like hypoxia (Marrif and Juurlink, 1999) and hypoglycemia (Bakken et al., 1998), and during periods of higher brain activation (Kasischke et al., 2004). The latter occurs when neurons have depleted their metabolic energy reserves and astrocytes compensate using their glycolytic capacity (Brown and Ransom, 2014).

5. Astrocytic antioxidant responses

It is well-understood that the health and function of neurons is tightly linked to that of astrocytes. This is manifest in the robust metabolic exchange between neurons and astrocytes mentioned previously; further examples of which include: glutathione redox (Dringen and Hirrlinger, 2003), glucose uptake (Bélanger et al., 2011), ion recycling (reviewed in (Verkhratsky et al., 2019)), and lipid transport (Ioannou et al., 2019). When environmental toxicants penetrate the blood-brain barrier, astrocytic endfeet abutting the vasculature place these cells as the primary defense against xenobiotic penetrance into the CNS.

5.1. Nrf2-mediated responses

Referred to as the "master regulator" of antioxidant genes, the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) is an important component of cellular responses to oxidative stress. Under basal conditions, Nrf2 levels are low because this protein is bound in the cytoplasm both by its negative regulator, Kelch-like erythroid cell-derived protein (Keap 1) and by Cullin 3 which ubiquitinates Nrf2 leading to rapid degradation. When cells experience oxidative stress, the Keap1-Cullin 3 interactions are disrupted leading to an increase in cytosolic Nrf2, which is subsequently translocated to the nucleus where it binds to the cognate antioxidant response element (ARE) in the upstream promoter region of antioxidant genes. Transcription of these cytoprotective genes initiated by Nrf2 has significant positive consequences in protecting cells, including astrocytes, from highly reactive peroxides, quinones, heme, and xenobiotic electrophiles (reviewed in (Vargas and Johnson, 2009)).

Pertinent to this review, astrocytes exhibit a robust Nrf2-mediated response to oxidative stressors (reviewed in (Liddell, 2017)). Since astrocytes are the most abundant glial cell and are in intimate contact with other glial cells, endothelial cells, and neurons, this quick antioxidant response to both endogenous and exogenous oxidative stressors is critical for brain health. It is interesting to consider that during normal aging, transcriptomic and epigenetic studies report that glial cells are in a more inflammatory state (Lu et al., 2004).

While in humans this is merely a correlation, rodent studies show that the antioxidant ARE-mediated response is impaired with age (Boisvert et al., 2018; Kubben et al., 2016). Furthermore, Nrf2 knockout mice exhibit widespread astrogliosis and transcriptomes that mirror aging mice (Rojo et al., 2017). The specific changes ascribed to astrocytes suggest that these cells adopt a more robust A1-reactive phenotype, for example aged astrocytes express more complement C3, a protein important for complement-mediated synaptic loss (Clarke et al., 2018). Taken together and reviewed in detail elsewhere (Palmer and Ousman, 2018), aged astrocytes display aberrant responses to signals (i.e., cytokines and chemokines) from other CNS cells (i.e., neurons, microglia and endothelial cells) and have a diminished capacity to maintain CNS homeostasis.

Early evidence for this pathway's involvement in neurodegenerative disease was found in post-mortem PD brain tissue, where increases in ARE-genes are apparent (Schipper et al., 1998). For example, NAD(P)H quinone dehydrogenase-1 (NQO1), heme oxygenase-1 (HO1), and glutathione peroxidase are elevated in PD post-mortem brains and are highest in regions particularly affected in this disorder (Power et al., 2002; Schipper et al., 1998; Van Muiswinkel et al., 2004). Furthermore, nuclear accumulation of Nrf2 is more apparent in the substantia nigra of PD brains when compared with brains from normal, Alzheimer's disease, and Lewy body variant of AD subjects (Ramsey et al., 2007). However, the post-mortem story is not clear-cut as other studies demonstrate that some ARE genes like glutathione peroxidase-1 show increased expression in microglia but not in neurons or astrocytes (Power and Blumbergs, 2009) while nonselenium glutathione peroxidase is increased in PD and dementia with Lewy body disease astrocytes (Power et al., 2002).

Nearly all neurodegenerative disorders have an inflammatory component and this type of microenvironment is known to promote an A1-astrocyte phenotype, which is perpetuated by surrounding glia. A

normal homeostatic astrocyte response to an inflammatory stimulus includes increased GSH release but Oksanen et al. using presenilin 1 (PSEN1) mutant AD patient iPSC-derived astrocytes demonstrated that diseased astrocytes do not increase GSH release (Oksanen et al., 2020). This group also showed that increasing the Nrf2 pathway by lenti-viral overexpression of Nrf2 or the use of a naturally occurring isothiocyanate incited an anti-inflammatory and anti-oxidative response in the AD astrocytes (Oksanen et al., 2020). Together this work supports that augmentation of the antioxidant response is a potential therapeutic target for neurodegenerative disorders. In fact, the Nrf2 pathway is a druggable target with a number of activators under clinical and preclinical investigation including dimethyl fumarate and sulforaphane (reviewed in (Cuadrado et al., 2019)) for disorders like multiple sclerosis, Friedreich's ataxia, ALS, and PD.

5.2. Glutathione

Glutathione, the most abundant non-protein thiol in mammalian cells, is a soluble tripeptide (synthesized from glutamate, cysteine and glycine) antioxidant molecule, the reduced nucleophilic form (GSH) of which is typically kept in large cytosolic reserves to be readily oxidized in the presence of reactive oxygen species (ROS) to form glutathione disulfide (GSSG). Glutathione synthesis is dependent on the consecutive action of two ATP-consuming reactions: in the first, rate-limiting step, glutamate-cysteine ligase (GCL) conjugates glutamate and cysteine to form γ-glutamylcysteine (γGluCys); in the second step, GSH synthase (GSS) ligates γGluCys to glycine to form GSH (Fig. 1).

Intracellular GSH acts as an ROS scavenger and, in the process of deactivating oxidants and radicals, generates GSSG. As such, the ratio of GSSG:GSH is a metric of oxidative stress and cellular health. The detoxification actions of GSH act through several mechanisms, including reduction of hydrogen peroxide (H_2O_2) to water (H_2O) and direct conjugation of certain xenobiotic compounds for detoxification. The major antioxidant function of the glutathione system consists of the reduction of peroxides, which is catalyzed by glutathione peroxidases (GPx), during which GSH is oxidized to form GSSG. To complete the redox cycle, GSSG is reduced back to form GSH using an electron from nicotinamide adenine dinucleotide phosphate (NADPH). The glutathione system utilizes glutathione S-transferases to form glutathione S-conjugates to detoxify xenobiotics, which are then exported from the cell through multidrug resistance proteins (MRPs). The astrocytic glutathione systems have been extensively studied and reviewed by Ralf Dringen and Johannes Hirrlinger (Dringen and Hirrlinger, 2003).

Primary astrocytes have intracellular GSH concentrations of 8−10 mM, which places them amongst the highest concentration for mammalian cells (Dringen and Hirrlinger, 2003; Raps et al., 1989) and the highest for brain cells. Importantly, *in vitro*evidence suggests that astrocytes are the only brain cell known to release GSH (Dringen and Hirrlinger, 2003). Glutathione dysregulation has been implicated in the context of several neurodegenerative diseases. In PD, glutathione depletion in the substantia nigra is one post-mortem pathological sign (Sofic et al., 1992); in AD, where oxidative stress is one of the causative factors implicated in disease pathogenesis, peripheral lymphocytes have decreased GSH and increased GSSG levels (Calabrese et al., 2007). Furthermore, dysfunction in the glutathione system is linked to disruption of many cellular pathways implicated in neurodegenerative disease pathogenesis, including protein aggregation and mitochondrial dysfunction.

6. Environmental toxicants and astrocytes

The combination of the localization of astrocytic endfeet to the BBB and their robust detoxification machinery places astrocytes in the first line of defense against xenobiotic penetrance of the CNS. Another example of the robust antioxidant and xenobiotic detoxification capacity of these cells is evident in their expression of multiple cytochrome P450 (CYP) isoforms. This suggests that the astrocytic CYP system is engaged at the BBB as compounds in systemic circulation gain access to the CNS. While there is limited data on the specific response of astrocytes to many toxicants, here we review a subset of the existing literature investigating the impact of a range of synthetic compounds on astrocytic and function.

6.1. Trace metals and ammonia

Exposure to manganese, a heavy metal, has long been linked to neurotoxicity and a Parkinson's-like syndrome including motor, cognitive and affective dysfunction, that mechanistically involves mitochondrial dysfunction leading to bioenergetic deficit (Olanow, 2004). While manganese is an essential trace metal and is necessary for many vital biochemical reactions in all tissues and cells, astrocytes specifically contain high-capacity manganese transporters (Marta and Aschner, 2013) and therefore have preferential efflux of this element, as well as the ability to sequester manganese (Aschner et al., 1992). Manganese exposure results in cell swelling in cultured astrocytes, a morphological change also found in Alzheimer's disease and hepatocerebral diseases (Hazell, 2002; Rama Rao et al., 2007).

Intracellularly, excess manganese interferes with a host of cellular processes including the glutamate-glutamine cycle and glutathione synthesis, leading to a reduction in glutamate uptake and a down-regulation of the excitatory amino acid transporter-1 (EAAT1; also referred to as the glutamate aspartate transporter [GLAST]) and GLT-1 (Mutkus et al., 2005) and glutamine transporters (Sidoryk-Węgrzynowicz et al., 2009). Importantly, manganese interacts with the astrocyte-abundant enzyme pyruvate carboxylase which, through its catalysis of the carboxylation of pyruvate to oxaloacetate, has a critical role in anaplerosis for the TCA cycle (Mildvan et al., 1966). The astrocytic metabolic processes impaired by manganese toxicity affect both primary glial function as well as neuronal functions that are dependent on functioning astrocyte metabolism. As such, impairment of astrocytic metabolic processes by manganese toxicity results in both direct neuronal dysfunctional as well as secondary dysfunction derived from compounding effects.

Similarly, ammonia (a compound of nitrogen and hydrogen) which can enter the brain via portal vein circulation following liver failure, leads to neurological sequelae including edema (Felipo and Butterworth, 2002). Astrocytic swelling is characteristic of liver-failure induced brain ammonia levels; astrocytes are the only brain cells capable of detoxifying ammonia through the glutamate-glutamine cycle, specifically with glutamine synthetase as a catalyst (Norenberg et al., 2005). Data from *in vitro* studies suggests that ammonia-induced astrocytic swelling is driven by the oxidative stress and mechanistically involves mitogen-activated protein kinase (MAPK) phosphorylation (Jayakumar et al., 2006a). This swelling (also observed in manganese toxicity) implicates AQP4 in addition to the glutamate-glutamine cycle and is thought to ultimately disrupt homeostasis and result in dysfunctional glutamatergic neurotransmission (Jayakumar et al., 2006b; Rama Rao et al., 2007).

Inorganic arsenic (As), from both anthropogenic and naturally occurring sources, exists as a potent environmental toxin in soil, air, and notably water, where it is a global contaminant (Amini et al., 2008). Exposure to arsenate (pentavalent arsenic [iAs^V]) and arsenite (trivalent arsenic [iAs^{III}]), the toxic inorganic arsenic species, are linked to severe health effects including CNS dysfunction (Prakash et al., 2016; Thomas et al., 2001). This includes cognitive impairments, developmental neurotoxicity (Tyler and Allan, 2014; Vahidnia et al., 2007) and neurodegenerative diseases including Alzheimer's (Gong and O'Bryant, 2010) and Parkinson's disease (Felix et al., 2005). Mechanistically, it is hypothesized that arsenate is structurally similar and able to substitute for phosphate in its biological actions and structures (Tawfik and Viola, 2011).

While little is known about the effect of arsenic species on astrocytes *in vivo*, from primary culture experiments it appears that arsenic species are taken up by astrocytes through an unknown mechanism.

Interestingly, GLUT1 catalyzes uptake of arsenite in *Saccharomyces cerevisiae* and *Xenopus laevis* oocytes (Liu et al., 2006) but inhibits glucose uptake and GLUT1 trafficking in human lymphocytes (Pánico et al., 2019). Arsenate and arsenite have been shown to stimulate glycolysis in astrocytes (Dringen et al., 2016) as well as increase GSH export through an MRP1-mediated pathway (Meyer et al., 2013). This evidence suggests that, as astrocytic metabolic pathways are engaged by arsenic species, astrocytic metabolic dysfunction is implicated in the mechanism by which exposure to arsenic species results in CNS deficits (reviewed in (Dringen et al., 2016)).

6.2. Chlorinated compounds

Organochlorines are a class of chlorinated hydrocarbons with wide-ranging applications and levels of toxicity. Organochlorine applications include: pesticides, insecticides, and myriad industrial purposes (for example: plasticizers and coolant). Importantly, chlorination of a hydrocarbon increases its lipophilicity and thereby its BBB penetrance, making these compounds powerful infiltrators of the CNS. Despite the well-documented toxicity of several members of this class, their effect on astrocytes is comparatively not well-studied.

Chlorpyrifos is a neurotoxic chlorinated organophosphate insecticide still widely used at the time of this publication. Several studies have found associations between chlorpyrifos exposure and decreases in full-scale IQ and working memory (Bouchard et al., 2011; Rauh et al., 2011), autism spectrum disorder (Shelton et al., 2014), and structural changes (Rauh et al., 2012). Chlorpyrifos performs its insecticide function through contact, inhalation, or ingestion and causes neurotoxicity by inhibiting acetylcholinesterase. This inhibition in turn increases the half-life of the neurotransmitter, acetylcholine, leading to hyperactivity/overstimulation-induced cell death. Additionally, chlorpyrifos exposure causes disruption of the BBB, impairment of molecular pathways (Wu et al., 2017), neural proliferation and differentiation. Importantly, astrocytes have been shown to be neuroprotective against chlorpyrifos exposure using a human pluripotent stem cell-derived astrocyte population. Specifically, this neuroprotection (in the form of neurite outgrowth) appears to be conferred through engagement of the astrocytic P450 system (Wu et al., 2017).

TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) is the most potent of the dibenzodioxins (or "dioxins") and as a contaminant in Agent Orange it contributed significantly to the biological toxicity and carcinogenicity associated with this chemical agent. Like many chlorinated organic compounds, TCDD is lipid-soluble and preferentially accumulates in fatty tissues, including the brain. Dioxin canonically signals through the aryl hydrocarbon receptor (AHR), which is thought to mediate TCDD's toxicity. Engagement of AHRs promotes xenobiotic response element activity in a number of genes including CYP1A1 (Swanson, 2002). TCDD also induces astrogliosis and promotes the secretion of TNFα as well as nuclear factor-κB (NFκB) activation (Zhang et al., 2014).

Polychlorinated biphenyls (PCBs) represent a large class of organochlorines, with variant mechanisms of action depending on the degree and location of the chlorine atoms on the biphenyl rings. PCBs were produced internationally from approximately 1930 until restricted by the Stockholm Convention on Persistent Organic Pollutants (POPs) in 2001, although several entities including the United States Environmental Protection Agency and the European Commission enacted earlier bans. Despite these bans, PCBs are still prevalent in the environment due to several of their biochemical properties, including lipophilicity and long half-lives. PCBs accumulate in lipid-rich tissues, such as the brain, where their detection post-mortem is linked to several diseases and symptoms, including Parkinson's disease (Hatcher-Martin et al., 2012) and cognitive decline (Bouchard et al., 2014). While PCBs have been associated with oxidative stress and cellular dysfunction in several animal models (Hennig et al., 1999; Lyng et al., 2007; Seegal et al., 1994) as well as neuronal and glial-like cell lines (Lee et al., 2006; Lee and Opanashuk, 2004), at the time of this publication there is no research investigating the impact of these ubiquitous compounds on astrocytes.

6.3. Fluorinated compounds

Fluorinated organic substances (identified as a group as per- and polyfluoroalkyl substances [PFAs] or perfluorinated compounds [PFCs]) are another category of man-made compounds found extensively throughout the environment. In addition to reproductive and developmental effects, cancer, and thyroid disruption, PFAs are linked to ADHD and spatial memory deficits (Hoffman et al., 2010; Long et al., 2013).

PFA/PFCs, including compounds like perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA), are used for industrial and commercial purposes ranging from non-stick coatings on cookware, paints, food packaging, and some sources of drinking water. They are resistant to degradation, in part due to the high bond-strength of the carbon-fluorine bond and their ability to bioaccumulate, which is determined by the length of carbon chain (Conder et al., 2008). Importantly, PFC bioaccumulation is distinct from most other halogenated toxicants as they principally accumulate in protein rich tissues as opposed to lipid rich tissues where chlorinated and brominated compounds accumulate (Butt et al., 2010; Weschler, 2009). This partitioning is an important factor in determining overall as well as specific organ toxicity.

With respect to astrocyte health, PFOS increases astrocytic apoptosis, and the expression of the gap junction protein, connexin-43, while reducing mitochondrial membrane potential (Dong et al., 2015). PFOS also elicits apoptosis of rat primary hippocampal neurons, with astrocyte-derived D-serine involvement (Yu et al., 2020), increased GFAP reactivity, and augmented NFκB-dependent interleukin-1β (IL-1β) secretion (Chen et al., 2018). PFOS-derived BBB disruption is due to decreases in tight-junction related protein expression, and ultimately leads to increased AQP4 and S100 calcium binding protein (S100B) expression in BBB-associated astrocytes (Yu et al., 2020). Rats exposed to PFOS prenatally showed increased expression of astrocyte activation markers (glial fibrillary acidic protein [GFAP] and S100BB) in the hippocampus and cortex (Zeng et al., 2011).

7. Conclusions

Importantly, as the focus of understanding the processes underlying CNS function continues to expand to encompass glial cells, glial-neuronal connections, and micro-environments shaped by the coordination of cells and their interactions, it is important to consider external factors that can disrupt this delicate homeostatic machinery. These external factors can present as a range of synthetic and natural, biological and chemical compounds. Synthetic chemical compounds are prevalent in our environment as a result of production in mass quantities, ubiquitous use, and often poor disposal practices. The history of industrialization is inextricable from the repeated failure of society to anticipate and account for the ways in which the mass manufacturing and eventual destruction of toxicants catalyzes an internecine cycle of environmental and human devastation.

Most neurodegenerative diseases have a far greater number of sporadic cases compared to familial/genetic cases, suggesting an impact of environmental factors on the pathogenesis of disease. As age is the strongest risk factor for many of these diseases, researchers have studied (at levels ranging from molecular to epidemiological) the ability of long-term exposure to toxicants to result in neurodegeneration later in life. As our understanding of neurodegenerative diseases, and the underlying mechanisms, evolves to include glial-specific processes more focused research on astrocytic metabolism is required.

Here, we reviewed the astrocyte-specific toxicant studies, with a focus on metabolic processes. While toxicant exposure results in complex and multi-faceted dysfunction, focusing on astrocytic metabolism, the function of which is critical for CNS homeostasis, enables us to study the engagement of specific pathways involved in a more global response.

Ammonia and manganese promote the reduction of the EAAT1 glutamate transporter as well as ensuing dysfunction of the glutamate-glutamine cycle linking astrocytes and neurons. As the organochlorines reviewed (PCBs and TCDD) have the propensity to accumulate in lipid membranes, it is possible that disruption of the membrane-bound glutamate transporters is involved in their toxicity.

Since the metabolism of astrocytes is indissociably connected to neuronal health and synaptic function, it is critical that our understanding of the impact of environmental toxicants on human health include this heretofore understudied aspect. From other metabolically linked disorders, such as diabetes, it is clear that environmental toxicant exposure can result in glucose dysfunction, including involvement of the GLUT1 transporter. Within the CNS, this transporter is astrocyte-specific, suggesting an overlap of peripheral and astrocytic mechanisms. Furthermore, engagement of the CYP detoxification system, which is robustly expressed in astrocytes as part of their role as the primary defense against xenobiotic penetrance into the CNS, suggests that astrocytes in particular are crucial for a system-wide response to toxicants. Importantly, systems that rely on astrocytes, such as glymphatic system clearance (Jiang et al., 2017; Zhang et al., 2019) and blood-brain barrier function (Acharya et al., 2013) are disrupted in diabetes, which is known to cause cognitive deficits. When viewed in conjunction with the perturbation of metabolic processes (such as glucose uptake) in diabetes as a result of environmental toxicant exposure, these pathological commonalities suggest astrocytic dysfunction as a possible nexus of CNS and peripheral disease. Overall, evidence is mounting that astrocytic metabolism is important for the response to and neutralization of environmental toxicants within the CNS. Further research into the specific pathways involved and the overlap of mechanisms with peripheral diseases will expand our understanding in an important direction.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgements

The schematic was created using BioRender.com. This work was supported by NIH/NINDS T32NS041218 and Georgetown University Biomedical Graduate Education (M.S.M).

References

Han, X., Chen, M., Wang, F., Windrem, M., Wang, S., Shanz, S., Xu, Q., Oberheim, N.A., Bekar, L., Betstadt, S., Silva, A.J., Takano, T., Goldman, S.A., Nedergaard, M., 2013. Forebrain engraftment by human glial progenitor cells enhances synaptic plasticity and learning in adult mice. Cell Stem Cell 12, 342–353. https://doi.org/10.1016/j.stem.2012.12.015.

Abbott, N.J., Rönnbäck, L., Hansson, E., 2006. Astrocyte-endothelial interactions at the blood-brain barrier. Nat. Rev. Neurosci. https://doi.org/10.1038/nrn1824.

Abbott, N.J., Pizzo, M.E., Preston, J.E., Janigro, D., Thorne, R.G., 2018. The role of brain barriers in fluid movement in the CNS: is there a 'glymphatic' system? Acta Neuropathol. https://doi.org/10.1007/s00401-018-1812-4.

Acharya, N.K., Levin, E.C., Clifford, P.M., Han, M., Tourtellotte, R., Chamberlain, D., Pollaro, M., Coretti, N.J., Kosciuk, M.C., Nagele, E.P., Demarshall, C., Freeman, T., Shi, Y., Guan, C., MacPhee, C.H., Wilensky, R.L., Nagele, R.G., 2013. Diabetes and hypercholesterolemia increase blood-brain barrier permeability and brain amyloid deposition: Beneficial effects of the LpPLA2 inhibitor darapladib. J. Alzheimers Dis. 35, 179–198. https://doi.org/10.3233/JAD-122254.

Agulhon, C., Petravicz, J., McMullen, A.B., Sweger, E.J., Minton, S.K., Taves, S.R., Casper, K.B., Fiacco, T.A., McCarthy, K.D., 2008. What Is the Role of Astrocyte Calcium in Neurophysiology? Neuron. https://doi.org/10.1016/j.neuron.2008.09.004.

Allen, N.J., Eroglu, C., 2017. Cell biology of astrocyte-synapse interactions. Neuron. https://doi.org/10.1016/j.neuron.2017.09.056.

Amini, M., Abbaspour, K.C., Berg, M., Winkel, L., Hug, S.J., Hoehn, E., Yang, H., Johnson, C.A., 2008. Statistical modeling of global geogenic arsenic contamination in groundwater. Environ. Sci. Technol. 42, 3669–3675. https://doi.org/10.1021/es702859e.

Amiry-Moghaddam, M., Ottersen, O.P., 2003. The molecular basis of water transport in the brain. Nat. Rev. Neurosci. 4, 991–1001. https://doi.org/10.1038/nrn1252.

Araque, A., Parpura, V., Sanzgiri, R.P., Handon, P.G., 1999. Tripartite synapses: glia, the unacknowledged partner. Trends Neurosci. 22, 208–215.

Aschner, M., Gannon, M., Kimelberg, H.K., 1992. Manganese uptake and Efflux in cultured rat astrocytes. J. Neurochem. 58, 730–735. https://doi.org/10.1111/j.1471-4159.1992.tb09778.x.

Attwell, D., Buchan, A.M., Charpak, S., Lauritzen, M., MacVicar, B.A., Newman, E.A., 2010. Glial and neuronal control of brain blood flow. Nature. https://doi.org/10.1038/nature09613.

Bakken, I.J., White, L.R., Unsgård, G., Aasly, J., Sonnewald, U., 1998. [U-13C]glutamate metabolism in astrocytes during hypoglycemia and hypoxia. J. Neurosci. Res. 51, 636–645. https://doi.org/10.1002/(SICI)1097-4547(19980301)51:5<636::AID-JNR11>3.0.CO;2-0.

Barnes, K., Ingram, J.C., Porras, O.H., Barros, L.F., Hudson, E.R., Fryer, L.G.D., Foufelle, F., Carling, D., Hardie, D.G., Baldwin, S.A., 2002. Activation of GLUT1 by metabolic and osmotic stress: potential involvement of AMP-activated protein kinase (AMPK). J. Cell. Sci. 115, 2433–2442.

Bazargani, N., Attwell, D., 2016. Astrocyte calcium signaling: the third wave. Nat. Neurosci. https://doi.org/10.1038/nn.4201.

Bélanger, M., Allaman, I., Magistretti, P.J., 2011. Brain energy metabolism: focus on Astrocyte-neuron metabolic cooperation. Cell Metab. https://doi.org/10.1016/j.cmet.2011.08.016.

Bernardinelli, Y., Randall, J., Janett, E., Nikonenko, I., König, S., Jones, E.V., Flores, C.E., Murai, K.K., Bochet, C.G., Holtmaat, A., Muller, D., 2014. Activity-dependent structural plasticity of perisynaptic astrocytic domains promotes excitatory synapse stability. Curr. Biol. 24, 1679–1688. https://doi.org/10.1016/j.cub.2014.06.025.

Boisvert, M.M., Erikson, G.A., Shokhirev, M.N., Allen, N.J., 2018. The aging astrocyte transcriptome from multiple regions of the mouse brain, in: cell reports. Elsevier B.V. 269–285. https://doi.org/10.1016/j.celrep.2017.12.039.

Bossy-Wetzel, E., Schwarzenbacher, R., Lipton, S.A., 2004. Molecular pathways to neurodegeneration. Nat. Med. 10, S2. https://doi.org/10.1038/nm1067.

Bouchard, M.F., Chevrier, J., Harley, K.G., Kogut, K., Vedar, M., Calderon, N., Trujillo, C., Johnson, C., Bradman, A., Barr, D.B., Eskenazi, B., 2011. Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. Environ. Health Perspect. 119, 1189–1195. https://doi.org/10.1289/ehp.1003185.

Bouchard, M.F., Oulhote, Y., Sagiv, S.K., Saint-Amour, D., Weuve, J., 2014. Polychlorinated biphenyl exposures and cognition in older U.S. adults: NHANES (1999-2002). Environ. Health Perspect. 122, 73–78. https://doi.org/10.1289/ehp.1306532.

Brown, A.M., Ransom, B.R., 2007. Astrocyte glycogen and brain energy metabolism. Glia. https://doi.org/10.1002/glia.20557.

Brown, A.M., Ransom, B.R., 2014. Astrocyte glycogen as an emergency fuel under conditions of glucose deprivation or intense neural activity. Metab. Brain Dis. 30, 233–239. https://doi.org/10.1007/s11011-014-9588-2.

Burda, J.E., Bernstein, A.M., Sofroniew, M.V., 2016. Astrocyte roles in traumatic brain injury. Exp. Neurol. https://doi.org/10.1016/j.expneurol.2015.03.020.

Butt, C.M., Berger, U., Bossi, R., Tomy, G.T., 2010. Levels and trends of poly- and perfluorinated compounds in the arctic environment. Sci. Total Environ. https://doi.org/10.1016/j.scitotenv.2010.03.015.

Calabrese, V., Mancuso, C., Ravagna, A., Perluigi, M., Cini, C., De Marco, C., Allan Butterfield, D., Stella, A.M.G., 2007. In vivo induction of heat shock proteins in the substantia nigra following L-DOPA administration is associated with increased activity of mitochondrial complex I and nitrosative stress in rats: regulation by glutathione redox state. J. Neurochem. 101, 709–717. https://doi.org/10.1111/j.1471-4159.2006.04367.x.

Cannon, J.R., Greenamyre, J.T., 2011. The role of environmental exposures in neurodegeneration and neurodegenerative diseases. Toxicol. Sci. 124, 225–250. https://doi.org/10.1093/toxsci/kfr239.

Chai, H., Diaz-Castro, B., Shigetomi, E., Monte, E., Octeau, J.C., Yu, X., Cohn, W., Rajendran, P.S., Vondriska, T.M., Whitelegge, J.P., Coppola, G., Khakh, B.S., 2017. Neural circuit-specialized astrocytes: transcriptomic, proteomic, morphological, and functional evidence. Neuron 95, 531–549. https://doi.org/10.1016/j.neuron.2017.06.029 e9.

Chen, X., Nie, X., Mao, J., Zhang, Y., Yin, K., Sun, P., Luo, J., Liu, Y., Jiang, S., Sun, L., 2018. Perfluorooctane sulfonate mediates secretion of IL-1β through PI3K/AKT NF-κB pathway in astrocytes. Neurotoxicol. Teratol. 67, 65–75. https://doi.org/10.1016/j.ntt.2018.03.004.

Clarke, L.E., Liddelow, S.A., Chakraborty, C., Münch, A.E., Heiman, M., Barres, B.A., 2018. Normal aging induces A1-like astrocyte reactivity. Proc. Natl. Acad. Sci. 115, E1896–E1905. https://doi.org/10.1073/pnas.1800165115.

Conder, J.M., Hoke, R.A., De Wolf, W., Russell, M.H., Buck, R.C., 2008. Are PFCAs bioaccumulative? A critical review and comparison with regulatory criteria and persistent lipophilic compounds. Environ. Sci. Technol. https://doi.org/10.1021/es070895g.

Cuadrado, A., Rojo, A.I., Wells, G., Hayes, J.D., Cousin, S.P., Rumsey, W.L., Attucks, O.C., Franklin, S., Levonen, A.L., Kensler, T.W., Dinkova-Kostova, A.T., 2019. Therapeutic targeting of the NRF2 and KEAP1 partnership in chronic diseases. Nat. Rev. Drug Discov. https://doi.org/10.1038/s41573-018-0008-x.

Dienel, G.A., 2019. Brain glucose metabolism: integration of energetics with function. Physiol. Rev. 99, 949–1045. https://doi.org/10.1152/physrev.00062.2017.

Djukic, B., Casper, K.B., Philpot, B.D., Chin, L.S., McCarthy, K.D., 2007. Conditional knock-out of Kir4.1 leads to glial membrane depolarization, inhibition of potassium and glutamate uptake, and enhanced short-term synaptic potentiation. J. Neurosci. 27, 11354–11365. https://doi.org/10.1523/JNEUROSCI.0723-07.2007.

Dong, L., Yang, X., Gu, W., Zhao, K., Ge, H., Zhou, J., Bai, X., 2015. Connexin 43 mediates PFOS-induced apoptosis in astrocytes. Chemosphere 132, 8–16. https://doi.org/10.1016/j.chemosphere.2015.02.041.

Dringen, R., Hirrlinger, J., 2003. Glutathione pathways in the brain biological chemistry. Biol. Chem. 384, 505–516. https://doi.org/10.1515/BC.2003.059.
Dringen, R., Spiller, S., Neumann, S., Koehler, Y., 2016. Uptake, metabolic effects and toxicity of arsenate and arsenite in astrocytes. Neurochem. Res. 41, 465–475. https://doi.org/10.1007/s11064-015-1570-9.
Felipo, V., Butterworth, R.F., 2002. Neurobiology of ammonia. Prog. Neurobiol. https://doi.org/10.1016/S0301-0082(02)00019-9.
Felix, K., Manna, S.K., Wise, K., Barr, J., Ramesh, G.T., 2005. Low levels of arsenite activates nuclear factor-κB and activator protein-1 in immortalized mesencephalic cells. J. Biochem. Mol. Toxicol. 19, 67–77. https://doi.org/10.1002/jbt.20062.
Fleming, S.M., 2017. Mechanisms of gene-environment interactions in parkinson's disease. Curr. Environ. Heal. reports. https://doi.org/10.1007/s40572-017-0143-2.
Gibbs, M.E., Anderson, D.G., Hertz, L., 2006. Inhibition of glycogenolysis in astrocytes interrupts memory consolidation in young chickens. Glia 54, 214–222. https://doi.org/10.1002/glia.20377.
Gong, G., O'Bryant, S.E., 2010. The arsenic exposure hypothesis for alzheimer disease. Alzheimer Dis. Assoc. Disord. 24, 311–316. https://doi.org/10.1097/WAD.0b013e3181d71bc7.
Gordon, G.R.J., Mulligan, S.J., MacVicar, B.A., 2007. Astrocyte control of the cerebrovasculature. Glia. https://doi.org/10.1002/glia.20543.
Halassa, M.M., Fellin, T., Takano, H., Dong, J.H., Haydon, P.G., 2007. Synaptic islands defined by the territory of a single astrocyte. J. Neurosci. 27, 6473–6477. https://doi.org/10.1523/JNEUROSCI.1419-07.2007.
Harder, D.R., Zhang, C., Gebremedhin, D., 2002. Astrocytes function in matching blood flow to metabolic activity. News Physiol. Sci. 17, 27–31. https://doi.org/10.1152/physiologyonline.2002.17.1.27.
Hatcher-Martin, J.M., Gearing, M., Steenland, K., Levey, A.I., Miller, G.W., Pennell, K.D., 2012. Association between polychlorinated biphenyls and Parkinson's disease neuropathology. Neurotoxicology 33, 1298–1304. https://doi.org/10.1016/j.neuro.2012.08.002.
Hawkins, B.T., Davis, T.P., 2005. The blood-brain barrier/neurovascular unit in health and disease. Pharmacol. Rev. https://doi.org/10.1124/pr.57.2.4.
Hazell, A.S., 2002. Astrocytes and manganese neurotoxicity. Neurochem. Int. 41, 271–277. https://doi.org/10.1016/S0197-0186(02)00013-X.
Hennig, B., Slim, R., Toborek, M., Robertson, L.W., 1999. Linoleic acid amplifies polychlorinated biphenyl-mediated dysfunction of endothelial cells. J. Biochem. Mol. Toxicol. 13, 83–91. https://doi.org/10.1002/(sici)1099-0461(1999)13:2<83::aid-jbt4>3.0.co;2-7.
Hoffman, K., Webster, T.F., Weisskopf, M.G., Weinberg, J., Vieira, V.M., 2010. Exposure to polyfuoroalkyl chemicals and attention deficit/hyperactivity disorder in U.S. Children 12-15 years of age. Environ. Health Perspect. 118, 1762–1767. https://doi.org/10.1289/ehp.1001898.
Iadecola, C., 2017. The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. Neuron. https://doi.org/10.1016/j.neuron.2017.07.030.
Iliff, J.J., Wang, M., Liao, Y., Plogg, B.A., Peng, W., Gundersen, G.A., Benveniste, H., Vates, G.E., Deane, R., Goldman, S.A., Nagelhus, E.A., Nedergaard, M., 2012. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Sci. Transl. Med. 4 https://doi.org/10.1126/scitranslmed.3003748.
Iliff, J.J., Wang, M., Zeppenfeld, D.M., Venkataraman, A., Plog, B.A., Liao, Y., Deane, R., Nedergaard, M., 2013. Cerebral arterial pulsation drives paravascular CSF-Interstitial fluid exchange in the murine brain. J. Neurosci. 33, 18190–18199. https://doi.org/10.1523/JNEUROSCI.1592-13.2013.
Ioannou, M.S., Jackson, J., Sheu, S.H., Chang, C.L., Weigel, A.V., Liu, H., Pasolli, H.A., Xu, C.S., Pang, S., Matthies, D., Hess, H.F., Lippincott-Schwartz, J., Liu, Z., 2019. Neuron-astrocyte metabolic coupling protects against activity-induced fatty acid toxicity. Cell 177, 1522–1535. https://doi.org/10.1016/j.cell.2019.04.001 e14.
Jayakumar, A.R., Panickar, K.S., Murthy, C.R.K., Norenberg, M.D., 2006a. Oxidative stress and mitogen-activated protein kinase phosphorylation mediate ammonia-induced cell swelling and glutamate uptake inhibition in cultured astrocytes. J. Neurosci. 26, 4774–4784. https://doi.org/10.1523/JNEUROSCI.0120-06.2006.
Jayakumar, A.R., Rao, K.V.R., Murthy, C.R.K., Norenberg, M.D., 2006b. Glutamine in the mechanism of ammonia-induced astrocyte swelling. Neurochem. Int. 48, 623–628. https://doi.org/10.1016/j.neuint.2005.11.017.
Jiang, Q., Zhang, L., Ding, G., Davoodi-Bojd, E., Li, Q., Li, L., Sadry, N., Nedergaard, M., Chopp, M., Zhang, Z., 2017. Impairment of the glymphatic system after diabetes. J. Cereb. Blood Flow Metab. 37, 1326–1337. https://doi.org/10.1177/0271678X16654702.
Kacem, K., Lacombe, P., Seylaz, J., Bonvento, G., 1998. Structural organization of the perivascular astrocyte endfeet and their relationship with the endothelial glucose transporter: a confocal microscopy study. Glia 23, 1–10. https://doi.org/10.1002/(SICI)1098-1136(199805)23:1<1::AID-GLIA1>3.0.CO;2-B.
Kasischke, K.A., Vishwasrao, H.D., Fisher, P.J., Zipfel, W.R., Webb, W.W., 2004. Neural activity triggers neuronal oxidative metabolism followed by astrocytic glycolysis. Science (80-.) 305, 99–103. https://doi.org/10.1126/science.1096485.
Kubben, N., Zhang, W., Wang, L., Voss, T.C., Yang, J., Qu, J., Liu, G.H., Misteli, T., 2016. Repression of the antioxidant NRF2 pathway in premature aging. Cell 165, 1361–1374. https://doi.org/10.1016/j.cell.2016.05.017.
Lee, D.W., Opanashuk, L.A., 2004. Polychlorinated biphenyl mixture aroclor 1254-induced oxidative stress plays a role in dopaminergic cell injury. Neurotoxicology 25, 925–939. https://doi.org/10.1016/j.neuro.2004.05.005.
Lee, D.W., Gelein, R.M., Opanashuk, L.A., 2006. Heme-oxygenase-1 promotes polychlorinated biphenyl mixture aroclor 1254-induced oxidative stress and dopaminergic cell injury. Toxicol. Sci. https://doi.org/10.1093/toxsci/kfj052.
Liddell, J.R., 2017. Are astrocytes the predominant cell type for activation of Nrf2 in aging and neurodegeneration? Antioxidants. https://doi.org/10.3390/antiox6030065.
Liddell, J.R., Robinson, S.R., Dringen, R., Bishop, G.M., 2010. Astrocytes retain their antioxidant capacity into advanced old age. Glia 58, 1500–1509. https://doi.org/10.1002/glia.21024.
Liddelow, S.A., Barres, B.A., 2017. Reactive astrocytes: production, function, and therapeutic potential. Immunity. https://doi.org/10.1016/j.immuni.2017.06.006.
Liu, Z., Sanchez, M.A., Jiang, X., Boles, E., Landfear, S.M., Rosen, B.P., 2006. Mammalian glucose permease GLUT1 facilitates transport of arsenic trioxide and methylarsonous acid. Biochem. Biophys. Res. Commun. 351, 424–430. https://doi.org/10.1016/j.bbrc.2006.10.054.
Loaiza, A., Porras, O.H., Barros, L.F., 2003. Glutamate triggers rapid glucose transport stimulation in astrocytes as evidenced by real-time confocal microscopy. J. Neurosci. https://doi.org/10.1523/jneurosci.23-19-07337.2003.
Long, Y., Wang, Y., Ji, G., Yan, L., Hu, F., Gu, A., 2013. Neurotoxicity of perfluorooctane sulfonate to hippocampal cells in adult mice. PLoS One 8. https://doi.org/10.1371/journal.pone.0054176.
Lu, T., Pan, Y., Kao, S.Y., Li, C., Kohane, I., Chan, J., Yankner, B.A., 2004. Gene regulation and DNA damage in the ageing human brain. Nature 429, 883–891. https://doi.org/10.1038/nature02661.
Lyng, G.D., Snyder-Keller, A., Seegal, R.F., 2007. Polychlorinated biphenyl-induced neurotoxicity in organotypic cocultures of developing rat ventral mesencephalon and striatum. Toxicol. Sci. 97, 128–139. https://doi.org/10.1093/toxsci/kfm027.
MacAulay, N., Hamann, S., Zeuthen, T., 2004. Water transport in the brain: role of cotransporters. Neuroscience 129, 1029–1042. https://doi.org/10.1016/j.neuroscience.2004.06.045.
Marrif, H., Juurlink, B.H.J., 1999. Astrocytes respond to hypoxia by increasing glycolytic capacity. J. Neurosci. Res. 57, 255–260. https://doi.org/10.1002/(SICI)1097-4547(19990715)57:2<255::AID-JNR11>3.0.CO;2-6.
Marta, S.-W., Aschner, M., 2013. Role of astrocytes in manganese mediated neurotoxicity. BMC Pharmacol. Toxicol. https://doi.org/10.1186/2050-6511-14-23.
Meyer, N., Koehler, Y., Tulpule, K., Dringen, R., 2013. Arsenate accumulation and arsenate-induced glutathione export in astrocyte-rich primary cultures. Neurochem. Int. 62, 1012–1019. https://doi.org/10.1016/j.neuint.2013.03.014.
Mildvan, A.S., Scrutton, M.C., Utter, M.F., 1966. Pyruvate carboxylase. VII. A possible role for tightly bound manganese. J. Biol. Chem. 241, 3488–3498. https://doi.org/10.1016/S0021-9258(18)99859-5.
Murphy-Royal, C., Johnston, A.D., Boyce, A.K.J., Diaz-Castro, B., Institoris, A., Peringod, G., Zhang, O., Stout, R.F., Spray, D.C., Thompson, R.J., Khakh, B.S., Bains, J.S., Gordon, G.R., 2020. Stress gates an astrocytic energy reservoir to impair synaptic plasticity. Nat. Commun. 11 https://doi.org/10.1038/s41467-020-15778-9.
Mutkus, L., Aschner, J.L., Fitsanakis, V., Aschner, M., 2005. The in vitro uptake of glutamate in GLAST and GLT-1 transfected mutant CHO-K1 cells is inhibited by manganese. Biol. Trace Elem. Res. 107, 221–230. https://doi.org/10.1385/BTER:107:3:221.
Norenberg, M.D., Rama Rao, K.V., Jayakumar, A.R., 2005. Mechanisms of ammonia-induced astrocyte swelling. Metab. Brain Dis. 303–318. https://doi.org/10.1007/s11011-005-7911-7.
Oksanen, M., Hyötyläinen, I., Trontti, K., Rolova, T., Wojciechowski, S., Koskuvi, M., Viitanen, M., Levonen, A.L., Hovatta, I., Roybon, L., Lehtonen, Š, Kanninen, K.M., Hämäläinen, R.H., Koistinaho, J., 2020. NF-E2-related factor 2 activation boosts antioxidant defenses and ameliorates inflammatory and amyloid properties in human Presenilin-1 mutated Alzheimer's disease astrocytes. Glia 68, 589–599. https://doi.org/10.1002/glia.23741.
Olanow, C.W.W., 2004. Manganese-induced parkinsonism and parkinson's disease. Ann. N. Y. Acad. Sci. 1012, 209–223. https://doi.org/10.1196/annals.1306.018.
Olsen, M.L., Khakh, B.S., Skatchkov, S.N., Zhou, M., Lee, C.J., Rouach, N., 2015. New insights on astrocyte ion channels: critical for homeostasis and neuron-glia signaling. J. Neurosci. 35, 13827–13835. https://doi.org/10.1523/JNEUROSCI.2603-15.2015.
Otsu, Y., Couchman, K., Lyons, D.G., Collot, M., Agarwal, A., Mallet, J.M., Pfrieger, F.W., Bergles, D.E., Charpak, S., 2015. Calcium dynamics in astrocyte processes during neurovascular coupling. Nat. Neurosci. 18, 210–218. https://doi.org/10.1038/nn.3906.
Palmer, A.L., Ousman, S.S., 2018. Astrocytes and aging. Front. Aging Neurosci. https://doi.org/10.3389/fnagi.2018.00337.
Pánico, P., Juárez-Nájera, A., Iturriaga-Goyon, E., Ostrosky-Wegman, P., Salazar Ana, M., 2019. Arsenic impairs GLUT1 trafficking through the inhibition of the calpain system in lymphocytes. Toxicol. Appl. Pharmacol. 380 https://doi.org/10.1016/j.taap.2019.114700.
Papouin, T., Dunphy, J., Tolman, M., Foley, J.C., Haydon, P.G., 2017. Astrocytic control of synaptic function. Philos. Trans. R. Soc. B Biol. Sci 372. https://doi.org/10.1098/rstb.2016.0154.
Parpura, V., Basarsky, T.A., Liu, F., Jeftinija, K., Jeftinija, S., Haydon, P.G., 1994. Glutamate-mediated astrocyte-neuron signalling. Nature 369, 744–747. https://doi.org/10.1038/369744a0.
Pekny, M., Wilhelmsson, U., Pekna, M., 2014. The dual role of astrocyte activation and reactive gliosis. Neurosci. Lett. https://doi.org/10.1016/j.neulet.2013.12.071.
Pellerin, L., Magistretti, P.J., 1994. Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. Proc. Natl. Acad. Sci. U. S. A. 91, 10625–10629. https://doi.org/10.1073/pnas.91.22.10625.
Pellerin, L., Pellegri, G., Bittar, P.G., Charnay, Y., Bouras, C., Martin, J.-L., Stella, N., Magistretti, P.J., 1998. Astrocyte-Neuron Metabolic Pathways Evidence Supporting the Existence of an Activity-Dependent Astrocyte-Neuron Lactate Shuttle.

Power, J.H.T., Blumbergs, P.C., 2009. Cellular glutathione peroxidase in human brain: cellular distribution, and its potential role in the degradation of Lewy bodies in Parkinson's disease and dementia with Lewy bodies. Acta Neuropathol. 117, 63–73. https://doi.org/10.1007/s00401-008-0438-3.

Power, J.H.T., Shannon, J.M., Blumbergs, P.C., Gai, W.P., 2002. Nonselenium glutathione peroxidase in human brain: elevated levels in Parkinson's disease and dementia with Lewy bodies. Am. J. Pathol. 161, 885–894. https://doi.org/10.1016/S0002-9440(10)64249-6.

Prakash, C., Soni, M., Kumar, V., 2016. Mitochondrial oxidative stress and dysfunction in arsenic neurotoxicity: a review. J. Appl. Toxicol. https://doi.org/10.1002/jat.3256.

Quintanilla, R.A., Porras, O.H., Castro, J., Barros, L.F., 2000. Cytosolic [Ca2+] modulates basal GLUT1 activity and plays a permissive role in its activation by metabolic stress and insulin in rat epithelial cells. Cell Calcium 28, 97–106. https://doi.org/10.1054/ceca.2000.0135.

Rama Rao, K.V., Reddy, P.V.B., Hazell, A.S., Norenberg, M.D., 2007. Manganese induces cell swelling in cultured astrocytes. Neurotoxicology 28, 807–812. https://doi.org/10.1016/j.neuro.2007.03.001.

Ramsey, C.P., Glass, C.A., Montgomery, M.B., Lindl, K.A., Ritson, G.P., Chia, L.A., Hamilton, R.L., Chu, C.T., Jordan-Sciutto, K.L., 2007. Expression of Nrf2 in neurodegenerative diseases. J. Neuropathol. Exp. Neurol. 66, 75–85. https://doi.org/10.1097/nen.0b013e31802d6da9.

Raps, S.P., Lai, J.C.K., Hertz, L., Cooper, A.J.L., 1989. Glutathione Is Present in High Concentrations in Cultured Astrocytes but Not in Cultured Neurons.

Rasmussen, M.K., Mestre, H., Nedergaard, M., 2018. The glymphatic pathway in neurological disorders. Lancet Neurol. https://doi.org/10.1016/S1474-4422(18)30318-1.

Rauh, V., Arunajadai, S., Horton, M., Perera, F., Hoepner, L., Barr, D.B., Whyatt, R., 2011. Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. Environ. Health Perspect. 119, 1196–1201. https://doi.org/10.1289/ehp.1003160.

Rauh, V.A., Perera, F.P., Horton, M.K., Whyatt, R.M., Bansal, R., Hao, X., Liu, J., Barr, D.B., Slotkin, T.A., Peterson, B.S., 2012. Brain anomalies in children exposed prenatally to a common organophosphate pesticide. Proc. Natl. Acad. Sci. U. S. A. 109, 7871–7876. https://doi.org/10.1073/pnas.1203396109.

Rodríguez-Arellano, J.J., Parpura, V., Zorec, R., Verkhratsky, A., 2016. Astrocytes in physiological aging and Alzheimer's disease. Neuroscience. https://doi.org/10.1016/j.neuroscience.2015.01.007.

Rojo, A.I., Pajares, M., Rada, P., Nuñez, A., Nevado-Holgado, A.J., Killik, R., Van Leuven, F., Ribe, E., Lovestone, S., Yamamoto, M., Cuadrado, A., 2017. NRF2 deficiency replicates transcriptomic changes in Alzheimer's patients and worsens APP and TAU pathology. Redox Biol. 13, 444–451. https://doi.org/10.1016/j.redox.2017.07.006.

Sargis, R.M., 2014. The Hijacking of cellular signaling and the diabetes epidemic: mechanisms of environmental disruption of insulin action and glucose homeostasis. Diabetes Metab. J. https://doi.org/10.4093/dmj.2014.38.1.13.

Schipper, H.M., Liberman, A., Stopa, E.G., 1998. Neural heme oxygenase-1 expression in idiopathic Parkinson's disease. Exp. Neurol. 150, 60–68. https://doi.org/10.1006/exnr.1997.6752.

Schlageter, K.E., Molnar, P., Lapin, G.D., Groothuis, D.R., 1999. Microvessel organization and structure in experimental brain tumors: microvessel populations with distinctive structural and functional properties. Microvasc. Res. 58, 312–328. https://doi.org/10.1006/mvre.1999.2188.

Seegal, R.F., Bush, B., Brosch, K.O., 1994. Decreases in dopamine concentrations in adult, non-human primate brain persist following removal from polychlorinated biphenyls. Toxicology 86, 71–87. https://doi.org/10.1016/0300-483X(94)90054-X.

Shelton, J.F., Geraghty, E.M., Tancredi, D.J., Delwiche, L.D., Schmidt, R.J., Ritz, B., Hansen, R.L., Hertz-Picciotto, I., 2014. Neurodevelopmental disorders and prenatal residential proximity to agricultural pesticides: the charge study. Environ. Health Perspect. 122, 1103–1109. https://doi.org/10.1289/ehp.1307044.

Sidoryk-Węgrzynowicz, M., Lee, E., Albrecht, J., Aschner, M., 2009. Manganese disrupts astrocyte glutamine transporter expression and function. J. Neurochem. 110, 822–830. https://doi.org/10.1111/j.1471-4159.2009.06172.x.

Sofic, E., Lange, K.W., Jellinger, K., Riederer, P., 1992. Reduced and oxidized glutathione in the substantia nigra of patients with Parkinson's disease. Neurosci. Lett. 142, 128–130. https://doi.org/10.1016/0304-3940(92)90355-B.

Souza, D.G., Almeida, R.F., Souza, D.O., Zimmer, E.R., 2019. The astrocyte biochemistry. Semin. Cell Dev. Biol. https://doi.org/10.1016/j.semcdb.2019.04.002.

Swanson, H.I., 2002. DNA binding and protein interactions of the AHR/ARNT heterodimer that facilitate gene activation. Chem. Biol. Interact. 141, 63–76. https://doi.org/10.1016/S0009-2797(02)00066-2.

Tani, H., Dulla, C.G., Farzampour, Z., Taylor-Weiner, A., Huguenard, J.R., Reimer, R.J., 2014. A local glutamate-glutamine cycle sustains synaptic excitatory transmitter release. Neuron 81, 888–900. https://doi.org/10.1016/j.neuron.2013.12.026.

Tawfik, D.S., Viola, R.E., 2011. Arsenate replacing phosphate: alternative life chemistries and ion promiscuity. Biochemistry 50, 1128–1134. https://doi.org/10.1021/bi200002a.

Thomas, D.J., Styblo, M., Lin, S., 2001. The cellular metabolism and systemic toxicity of arsenic. Toxicol. Appl. Pharmacol. https://doi.org/10.1006/taap.2001.9258.

Tran, C.H.T., Peringod, G., Gordon, G.R., 2018. Astrocytes Integrate Behavioral State and Vascular Signals during Functional Hyperemia. Neuron 100, 1133–1148. https://doi.org/10.1016/j.neuron.2018.09.045 e3.

Tyler, C.R., Allan, A.M., 2014. The effects of arsenic exposure on neurological and cognitive dysfunction in human and rodent studies: a review. Curr. Environ. Heal. reports. https://doi.org/10.1007/s40572-014-0012-1.

Vahidnia, A., Van Der Voet, G.B., De Wolff, F.A., 2007. Arsenic neurotoxicity - A review. Hum. Exp. Toxicol. https://doi.org/10.1177/0960327107084539.

Van Muiswinkel, F.L., De Vos, R.A.I., Bol, J.G.J.M., Andringa, G., Jansen Steur, E.N.H., Ross, D., Siegel, D., Drukarch, B., 2004. Expression of NAD(P)H:quinone oxidoreductase in the normal and Parkinsonian substantia nigra. Neurobiol. Aging 25, 1253–1262. https://doi.org/10.1016/j.neurobiolaging.2003.12.010.

Vargas, M.R., Johnson, J.A., 2009. The Nrf2-ARE cytoprotective pathway in astrocytes. Expert Rev. Mol. Med. https://doi.org/10.1017/S1462399409001094.

Verkhratsky, A., Parpura, V., Vardjan, N., Zorec, R., 2019. Physiology of astroglia. Adv. Exp. Med. Biol. 45–91. https://doi.org/10.1007/978-981-13-9913-8_3.

Weber, B., Barros, L.F., 2015. The astrocyte: powerhouse and recycling center. Cold Spring Harb. Perspect. Biol. 7 https://doi.org/10.1101/cshperspect.a020396.

Weschler, C.J., 2009. Changes in indoor pollutants since the 1950s. Atmos. Environ. 43, 153–169. https://doi.org/10.1016/j.atmosenv.2008.09.044.

Wu, X., Yang, X., Majumder, A., Swetenburg, R., Goodfellow, F.T., Bartlett, M.G., Stice, S. L., 2017. Astrocytes are protective against chlorpyrifos developmental neurotoxicity in human pluripotent stem cell-derived astrocyte-neuron cocultures. Toxicol. Sci. 157, 410–420. https://doi.org/10.1093/toxsci/kfx056.

Yu, Y., Wang, C., Zhang, X., Zhu, J., Wang, L., Ji, M., Zhang, Z., Ji, X.M., Wang, S.L., 2020. Perfluorooctane sulfonate disrupts the blood brain barrier through the crosstalk between endothelial cells and astrocytes in mice. Environ. Pollut. 256 https://doi.org/10.1016/j.envpol.2019.113429.

Zeng, X.N., Sun, X.L., Gao, L., Fan, Y., Ding, J.H., Hu, G., 2007. Aquaporin-4 deficiency down-regulates glutamate uptake and GLT-1 expression in astrocytes. Mol. Cell. Neurosci. 34, 34–39. https://doi.org/10.1016/j.mcn.2006.09.008.

Zeng, H., Zhang, L., Li, Yyuan, Wang, Yjian, Xia, W., Lin, Y., Wei, J., Xu, Sqing, 2011. Inflammation-like glial response in rat brain induced by prenatal PFOS exposure. Neurotoxicology 32, 130–139. https://doi.org/10.1016/j.neuro.2010.10.001.

Zhang, Y., Nie, X., Tao, T., Qian, W., Jiang, S., Jiang, J., Li, A., Guo, A., Xu, G., Wu, Q., 2014. 2,3,7,8-Tetrachlorodibenzo-p-dioxin promotes astrocyte activation and the secretion of tumor necrosis factor-α via PKC/SSeCKS-dependent mechanisms. J. Neurochem. 129, 839–849. https://doi.org/10.1111/jnc.12696.

Zhang, L., Chopp, M., Jiang, Q., Zhang, Z., 2019. Role of the glymphatic system in ageing and diabetes mellitus impaired cognitive function. Stroke Vasc. Neurol. https://doi.org/10.1136/svn-2018-000203.

Zonta, M., Angulo, M.C., Gobbo, S., Rosengarten, B., Hossmann, K.A., Pozzan, T., Carmignoto, G., 2003. Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation. Nat. Neurosci. 6, 43–50. https://doi.org/10.1038/nn980.