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Astrocytes in Psychiatric Disorders

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Astrocytes in Psychiatric Disorders

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Part I
General Aspects of Astrogliopathology with Emphasis on Neurocognitive Disorders

Neuroglia in Psychiatric Disorders

Caterina Scuderi, Alexei Verkhratsky, Vladimir Parpura, and Baoman Li

Introduction: Definition, Classification, and Main Functions of Neuroglia

The human brain has a considerable complexity. In a rather limited volume, it contains a population of more than 200 billion neural cells, including neurones and neuroglia. Altogether, these neural cells form intricate networks connecting the various parts that make up this organ through trillions of chemical and electrical synapses. The concept of neuroglia was initially formalized by Rudolf Virchow who introduced it in the mid-1800s. According to Virchow, neuroglia was a "substance also which lies between the proper nervous parts, holds them together and gives the whole its form in a greater or lesser degree" (Virchow 1860). The neuroglia is present in both the peripheral nervous system (PNS) and the central nervous system (CNS) (Fig. 1). The PNS neuroglia arises from the neural crest, similarly to peripheral neurones, and is classified into Schwann cells (Kidd et al. 2013), satellite

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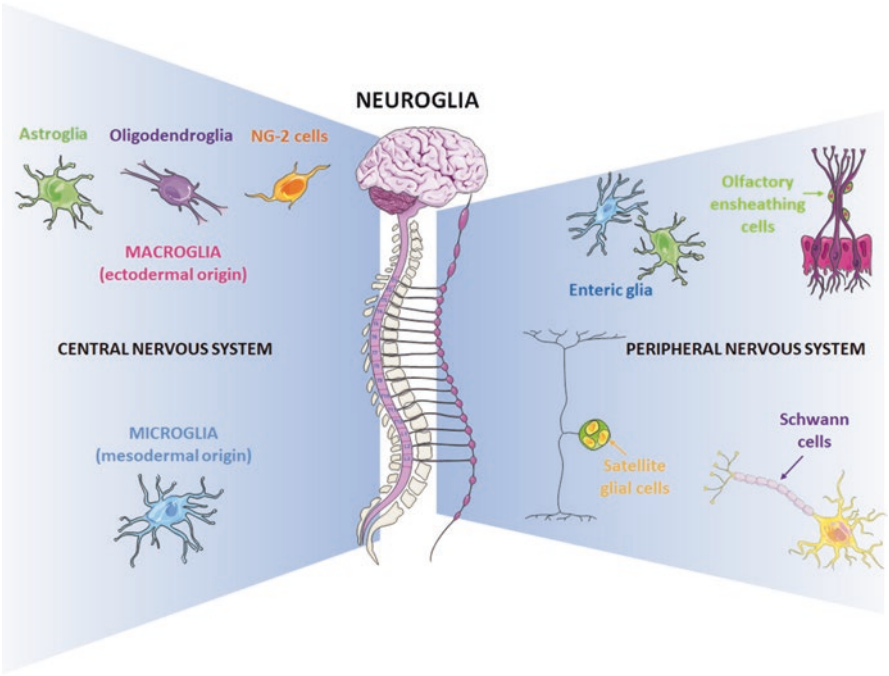

Fig. 1 Neuroglia classification

glial cells (Hanani and Verkhratsky 2021), olfactory ensheathing cells (Ruitenberg et al. 2006), and enteric glia (Grubisic et al. 2018). The neuroglia cells of the CNS are divided into macroglia cells (ectodermal, neuroepithelial origin) and microglia (mesodermal, myeloid origin) (Verkhratsky and Butt 2013). Macroglia is further classified into astroglia, oligodendroglia, and NG-2 glia, the latter also known as oligodendrocyte progenitor cells, or synantocytes, or polydendrocytes (Verkhratsky and Butt 2013). Each of these populations listed above can, in turn, be divided into further subtypes, making the complexity that these cells possess to parallel the multitude of functions they govern. The large number of subtypes of glial cells fueled for years the belief that in the human brain glial cells outnumber neurones by a factor of 10 up to 50 (Bear et al. 2007; Kandel et al. 2000). However, the views of numerical preponderance of glial cells in the brain and spinal cord with respect to the number of neurones have been proven erroneous, because none of the concepts that had been adopted as a demonstration of big glial numbers has been corroborated experimentally (Hilgetag and Barbas 2009; von Bartheld et al. 2016). It is generally agreed upon that the total number of neuronal and non-neuronal cells in the human brain is almost on par. Nonetheless, even if not in a linear manner, the evolution of the nervous system paralleled with trend of an increase in glia to neurone ratio (Verkhratsky et al. 2019), suggesting glial involvement in cerebral superior functions, although the largest numbers of glial cells are observed in the largest brains of whales and elephants.

The unifying fundamental function of all types of glial cells, regardless of their origin, structure, morphological appearance, and function, is the maintenance of the homeostasis of the nervous system (Verkhratsky and Butt 2013). This function is of crucial importance in the healthy brain, when neuroglia perform the normal housekeeping duties, as well as in pathology, when glial cells react to unusual stimuli and undergo morphofunctional modifications aimed at restoring brain homeostasis. Any deviation from this delicate equilibrium may have serious consequences in the correct development or functioning of the brain. The homeostatic support of neuroglia takes place at all levels of brain organization, thus allowing the brain to function properly.

Microglia

Microglia are the main type of immune cells that permanently reside in the CNS. Unlike all other brain parenchymal cells that have multiple neuroectodermal lineages, microglia originate from a mesodermal source. Microglia are of the myeloid origin, colonize the CNS very early in evolution, and are conserved across species (Ginhoux et al. 2010; Monier et al. 2007; Schlegelmilch et al. 2011; Swinnen et al. 2013; Verney et al. 2010). For a long time studies on microglia have been focused on their function as resident macrophages and their role in the immune response (Cartier et al. 2014; Prinz et al. 2011; Prinz and Priller 2014). Being the main immunocompetent cells of the nervous system, microglia fulfill fundamental defensive function by the virtue of their phagocytic capacity and ability to secrete numerous pro- and anti-inflammatory factors. Through phagocytosis, microglia can incorporate waste products, cellular debris, and pathogens (Nayak et al. 2014). Advances in the available technologies have enabled a better understanding of the microglial functions across different conditions (Tay et al. 2019). Microglia is fundamental for brain development, activity, and plasticity (Tay et al. 2017), including the creation and remodeling of synapses. Through the modulation of synapse number and synaptic activity, microglia can regulate the processes of learning, memory, and cognition (Weinhard et al. 2018). Microglia also regulate neurogenesis, neuronal density and connectivity, as well as neuronal survival and turnover (Shigemoto-Mogami et al. 2014). Most of these processes begun during the period of perinatal development and persist through to the late adolescence/adulthood (Sellner et al. 2016; Sierra et al. 2010; Ueno et al. 2013). Microglial functions are based on the scavenging of cellular debris as well as the intense exchange of communication between microglia and neurones, achieved through the production and release of numerous neurotrophic mediators (Tay et al. 2017). This former property explains the reason why microglial numerical preponderance occurs in areas containing debris or apoptotic neurones as well as in regions with high density of neural precursor cells where microglia can drive neuronal turnover during development (Ayata et al. 2018; Cunningham et al. 2013; Swinnen et al. 2013). Microglia can be considered as key contributors to normal brain functioning, mainly because these cells

regularly scan the surrounding environment and adapt their morphology and functions to restore homeostasis. Therefore, dysfunctions of microglial cells could have deleterious consequences at any stage of human life. During the pre- and perinatal brain development, the modification of microglial functions could impair essential processes such as neural connectivity and synaptic plasticity (Kettenmann et al. 2013). In the same way during adult life, changes to microglial functions could cause a remodeling of the neuronal circuits with serious consequences on learning and memory (Weinhard et al. 2018). In conclusion, dysfunctional microglia play a fundamental role in the onset, evolution, and outcome of neurological diseases throughout life span (Scuderi and Verkhratsky 2020; Tay et al. 2018).

Oligodendrocyte and NG-2 Glia

Oligodendrocytes are cells of fundamental importance for the CNS because they form the myelin sheath necessary for a fast and efficient transmission of the nervous impulse. Oligodendrocytes originate from the oligodendrocyte precursor cells (OPCs) that arise from multipotent neural stem cells (NSCs), mainly localized in the ventricular zones of the brain from which they migrate to the developing CNS where they become active oligodendrocytes. This process starts shortly before birth and continues throughout life (Bergles and Richardson 2015) as a significant amount of OPCs persists in the adult brain. These OPCs have been also identified as NG-2 glia because they express CSPG4, the NG2 chondroitin sulfate proteoglycan (Almeida and Lyons 2017). The differentiation of NG-2 glia into oligodendrocytes is essential for myelin repair in the adult brain (Ortiz et al. 2019), and for ensheathing new neuronal connections with myelin in response to new experiences (McKenzie et al. 2014; Xiao et al. 2016). These observations suggest that neurotransmission drives the differentiation of NG-2 glia and are consistent with the evidence that NG-2 glia exhibit a wide range of ion channels and neurotransmitter receptors (Larson et al. 2016), and respond to synaptic transmission (Bergles et al. 2000). Despite these findings, further studies are required to decipher how neuronal activity drives NG-2 glia conversion in oligodendrocytes. Indeed, data acquired so far demonstrated that blocking, or stimulating, synaptic signaling has only weak effects on NG-2 glia, suggesting that neurotransmitters alone are not sufficient to start oligodendrogenesis (Butt et al. 2019).

Several factors modulate OPC migration, proliferation, differentiation, and myelination (Elbaz and Popko 2019). These factors include extrinsic as well as intrinsic transcription factors, epigenetic modulators, and signaling pathways (Elbaz and Popko 2019). Oligodendrocytes express many receptors belonging to different classes suggesting that these cells receive impulses from different signaling pathways indispensable for their development and functions, mainly the formation of myelin (Butt et al. 2019; Habermacher et al. 2019; Kiray et al. 2016; Patel and Klein 2011). For instance, it has been demonstrated that the Wnt signaling controls OPC expansion throughout life (Azim et al. 2017) and that estrogen favors

oligodendrocyte differentiation and myelination by regulating cholesterol homeostasis (Voskuhl et al. 2019).

Myelin is mostly composed of lipids (about 70%, of which the primary component is cholesterol) and proteins (about 30%, of which the main components are the myelin basic protein and proteolipid protein) (Muller et al. 2013; Saher and Stumpf 2015). Although oligodendrocytes seem capable of de novo synthesis of cholesterol, it has been suggested that the lipid used to form the myelin sheath comes from astrocytes, as the blood-brain barrier (BBB) does not allow dietary cholesterol to enter the CNS (Kirayet al. 2016). Myelin also contains gap junctions formed by connexins, which are fundamental for ion homeostasis and axonal metabolism and integrity (Vejar et al. 2019). Besides the establishment of the optimal conditions for rapid electrical conduction, myelin is also required for axonal integrity (Alexandra et al. 2018). The underlying mechanisms are not fully clarified, but recent evidence indicates oligodendrocytes as essential for fulfilling axonal metabolic needs. They indeed provide glucose (Meyer et al. 2018) and lactate to axons (Funfschilling et al. 2012; Lee et al. 2012) depending on the axonal activity requirements (Micu et al. 2018; Saab et al. 2016).

Given the above, dysfunction or loss of oligodendroglia or of their ability to make the myelin sheath can cause devastating effects on CNS function and eventually lead to neuronal death. Moreover, the pleiotropism of factors involved in oligodendrocyte development and myelination helps to ensure that the disruption of any single factor does not result in their loss of function. On the other side, they represent multiple targets that could be involved in oligodendrocyte pathologies offering exciting new perspectives of research.

Astrocytes

Astroglia (to which astrocytes belong) are a class of highly heterogeneous in form and function neural cells of the ectodermal, neuroepithelial origin; these cells maintain homeostasis and defence of the CNS (Verkhratsky and Nedergaard 2018). Astrocytes reside in the white and gray matter of the brain and the spinal cord (Verkhratsky and Butt 2013). Numerous distinct morphological and functional subtypes of astrocytes have been identified, including (i) *protoplasmic astrocytes* of the gray matter; (ii) *fibrous astrocytes* of the white matter; (iii) *velate astrocytes*, localized in brain regions where neurones are small and densely packed (e.g., the olfactory bulb or the granular layer of the cerebellar cortex); (iv) *radial glia*, which are the pluripotent neural cell precursors that mostly disappear at birth; (v) *radial astrocytes*, which comprise the cerebellar Bergmann glia, the retinal Müller glia, radial glia-like neural stem cells of the neurogenic niches, and tanycytes; (vi) *pituicytes*, localized in the neurohypophysis; (vii) the iron-enriched astrocytes, named *Gomori astrocytes*, localized in the hypothalamus and the hippocampus; (viii) *perivascular astrocytes*, whose endfeet connect with blood vessels and are fundamental for the establishment of the glia limitans barriers; (ix) juxtavascular

astrocytes somata of which are in close apposition with blood vessels; (x) *ependymocytes*, which are choroid plexus cells, lining the ventricles and producing the cerebrospinal fluid, and retinal pigment epithelial cells, which line up the retinal space; and specialized astrocytes observed only in the brain of higher primates (including humans) which include (xi) i*nterlaminar astrocytes*, (xii) *polarized astrocytes*, and (xiii) *varicose projection astrocyte;* functions of all these types are still unclear (Colombo 2018; Verkhratsky et al. 2018, 2019).

The heterogeneity of astroglia correlates with the multiplicity of functions that they perform. For instance, astroglia (i) control the levels of neurotransmitters, ions, reactive oxygen species, and metabolites (Deitmer and Rose 1996; Hertz et al. 1999; Kirischuk et al. 2007; Kofuji and Newman 2004); (ii) drive neurogenesis (Verkhratsky and Nedergaard 2018); (iii) regulate synapse formation, pruning, and elimination (Kettenmann et al. 2011, 2013; Pfrieger 2010); (iv) form and maintain the myelin sheath (Butt et al. 2019; Kuhn et al. 2019); and (v) control the BBB and the blood flow (Abbott et al. 2010; Attwell et al. 2010) (Fig. 2). The type and relative number of astrocytes vary among brain regions (Verkhratsky et al. 2019). Despite their great variety of morphology and functions, all astrocytes are best at performing their homeostatic function. To this end, astrocytes cooperate to form, through gap junctions, cellular networks called syncytia, comprised of apposing membranes of adjacent astrocytes pierced by hundreds of intercellular channels or connexons (Giaume et al. 2010). Gap junctions represent highly specialized areas for the transport of second messengers, ions, and bioactive molecules (Houades et al. 2008; Roux et al. 2011). Networks between astrocytes and oligodendrocytes have been identified in both the hippocampus and the neocortex (Butt and Ransom 1989; Griemsmann et al. 2015; Pastor et al. 1998) and named "panglial syncytia."

Astrocytic membrane carries a multitude of receptors for neurotransmitters and neurohormones, ion channels, and membrane transporter systems. Astrocytes

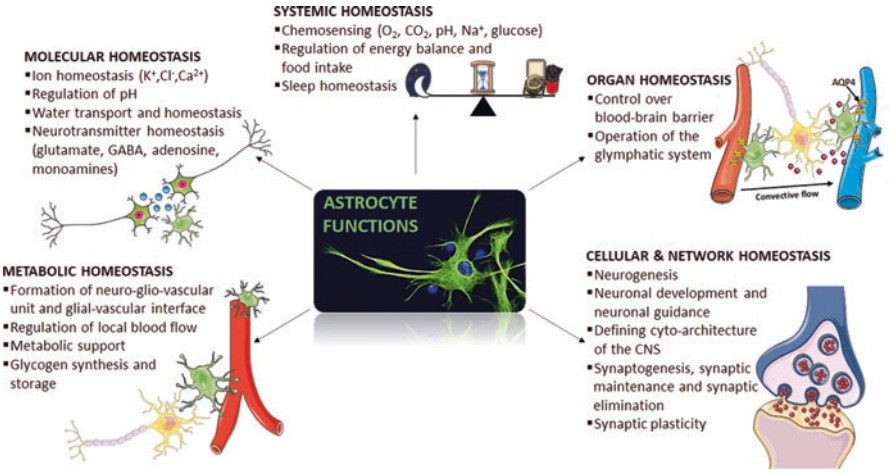

Fig. 2 Astrocytes as homeostatic cells of the CNS

integrate the signals from all other cells to operate their homeostatic function and foster neuronal activity. Channels for K^+ (voltage-independent, voltage-gated and Ca^{2+}-dependent K^+ channels), Na^+ (voltage-gated, specific type of Na^+ channels regulated by extracellular Na^+ concentration and epithelial Na^+ channels), and Ca^{2+} (voltage-gated, Orai, and Ca^{2+} release channels), as well as for many other ions, have been registered (for a comprehensive review, refer to Verkhratsky and Nedergaard 2018). Also, astrocytes express receptors for almost all neuroactive agents (Kettenmann and Zorec 2013; Verkhratsky 2010), including adenosine receptors (Dare et al. 2007; Pilitsis and Kimelberg 1998), purinoreceptors (Franke et al. 2001; Fumagalli et al. 2003; Verkhratsky et al. 2009), GABA receptors (MacVicar et al. 1989; Nilsson et al. 1993), glycine receptors (Kirchhoff et al. 1996; Pastor et al. 1995), acetylcholine receptors (Graham et al. 2003; Sharma and Vijayaraghavan 2001), monoamines receptors (Hertz et al. 2010; Miyazaki et al. 2004; Shelton and McCarthy 2000), cannabinoid receptors (Navarrete and Araque 2008; Navarrete and Araque 2010), and both ionotropic and metabotropic glutamate receptors (Lalo et al. 2006; Sun et al. 2013; Verkhratsky and Butt 2013; Verkhratsky and Chvatal 2020). Lastly, numerous membrane transporter systems for different ions and neuroactive substances complete the complex astrocytic machinery required to exert their homeostatic function, such as the Na^+-K^+ ATPase (Hertz et al. 2015), Ca^{2+}-ATPases (Verkhratsky and Nedergaard 2018), as well as plasmalemmal transporters for GABA (Ribak et al. 1996), glycine (Zafra et al. 1995), glutamate (Verkhratsky and Rose 2020), glutamine (Scalise et al. 2016), and monocarboxylates (Halestrap 2012). In this way, astrocytes control the CNS microenvironment by adjusting extracellular neurotransmitters, ions, and pH, regulating blood flow through the release of vasoactive molecules, and buffering reactive oxygen species (Parpura and Verkhratsky, 2012). It has been demonstrated the ability of a single astrocyte to be in contact with several neurones. In this way, they finely regulate synaptic transmission by tuning neurotransmitter levels in the synaptic cleft (Verkhratsky and Nedergaard 2018). Astrocytes are fundamental components of the BBB where their presence is essential for a protective function and the control of cerebral flow, thus regulating the communication between the CNS and the periphery (Verkhratsky and Parpura 2015). Astrocytes are also a part of the so-called gliocrine system, releasing around 200 molecules, mainly neurotrophic factors, and energy substrates, fundamental for the maintenance of CNS functions (Verkhratsky et al. 2016).

Given the above, all types of glial cells contribute to neuropathological developments. As astrocytes are a part of neural networks, interacting with neurones, with other glial cells, and with blood vessels, they are the key players in maintaining the structural and functional integrity of the brain tissue. The role of astrocytes in driving neuronal function and survival both in physiology and pathology has been widely documented (Verkhratsky and Nedergaard 2018). The hypothesis that astrocyte dysfunctions allow the creation of a disease-permissive context, which may favor neuronal deficits and death, has gained great attention in the recent years. Here, we provide a brief recap of the evidence accumulated so far on the active role

of astrocytes in neuropsychiatric disorders, which are discussed in detail in the following chapters.

Astrogliopathology in Neuropsychiatric Disorders

Considering the above-mentioned multiple homeostatic and supportive functions that astrocytes perform, it becomes clear that any changes in the physiological performance of these cells are having a role in the etiology or progression of neuropsychiatric pathologies. Astrocyte impairments can be generic or disease-specific, and they often differ depending on the stage of the disease (Pekny et al. 2016). To complicate this scenario, human diseases are frequently modified both by age and by the presence of other comorbidities. Schematically, we can divide astrogliopathies into three main categories: (i) reactive astrogliosis; (ii) astroglial atrophy, characterized by degeneration and loss of function; and (iii) pathological remodeling of astrocytes (Verkhratsky et al. 2017a, 2019) (Fig. 3). It should be remembered that all three of these reactions are considered pathological, as well as that they can occur simultaneously or singly.

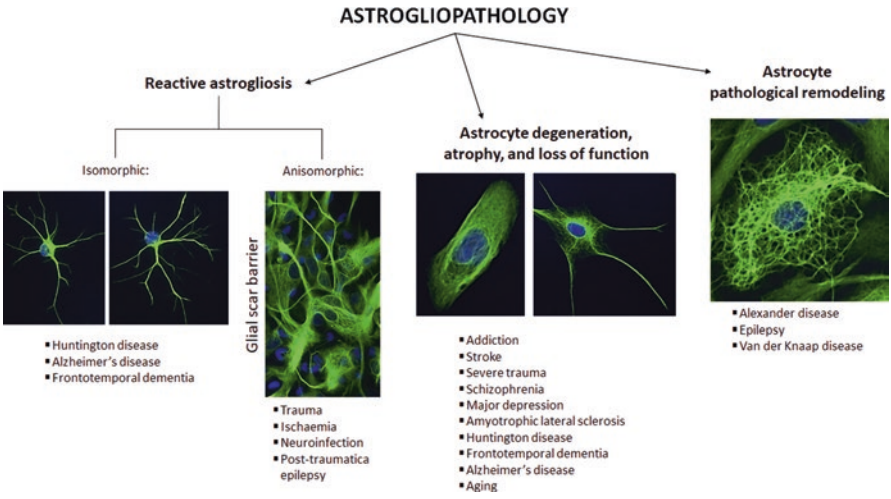

Fig. 3 Astrocyte contribution to neuropsychiatric disorders

Reactive Astrogliosis in Neuropsychiatric Disorders

Reactive astrogliosis represents the most studied type of astrocytic response (Escartin et al. 2021), which has been considered for a long time the stereotypic and universal response to pathology. According to the severity, reactive astrogliosis can be classified as mild to moderate astrogliosis, diffuse severe astrogliosis, and severe astrogliosis with scar formation (Sofroniew 2009, 2014). According to cellular morphology, two types of reactive astrogliosis have been identified: the isomorphic one, which is reversible and characterized by the preservation of the territorial astroglial domains, and the anisomorphic astrogliosis, characterized by a lack of maintenance of the territorial domains, presence of cell migration, territorial overlap, and ultimately scar formation (Pekny et al. 2016). Histopathologically, reactive astrocytes display hypertrophic extensions due to the upregulation of vimentin and glial fibrillary acidic protein (GFAP), two cytoskeletal intermediate filaments/proteins (Hol and Pekny 2015; Sofroniew 2014). Broadly speaking, reactive astrocytes undergo numerous morphological and functional modifications, acquiring different phenotypes that are believed to be disease specific (Pekny et al. 2016; Escartin et al. 2021).

Reactive astrogliosis is an evolutionary-conserved defensive program aimed at isolating the damaged region, increasing neuroprotection, and starting the reparation of the damaged nervous tissue, as well as the BBB. Growing experimental evidence supports this notion, demonstrating that the suppression of reactive astrogliosis often increases the extent of the traumatic brain injury, exacerbates post-traumatic synaptic loss, and aggravates disease progression (Li et al. 2008; Okada et al. 2006; Pekny et al. 1999, 2014, 2016). Thus, astrocytic reactivity is broadly considered neuroprotective, albeit in some circumstances, especially if sustained for a too long time, it can become a maladaptive process, the consequences of which may override the initial benefits.

Reactive astrogliosis has been widely documented in numerous neurological diseases, including multiple sclerosis, Alzheimer's disease, and autism spectrum disorders (Bronzuoli et al. 2018a, b; das Neves et al. 2020; Scuderi et al. 2018; Scuderi and Verkhratsky 2020; Tang et al. 2006; Zeidan-Chulia et al. 2014). Accumulating evidence indicates the presence of reactive astrocytes even in the course of some neuropsychiatric disorders. For instance, the astrocytic responses to chronic alcohol use may also lead to secondary activation of gliosis-like astrocyte responses (Miguel-Hidalgo 2009; Miguel-Hidalgo and Rajkowska 2003).

Astrocyte Degeneration, Atrophy, and Loss of Function in Neuropsychiatric Disorders

Astrodegeneration is characterized by morphological atrophy and functional asthenia of astrocytes. Thickness and extension of astrocyte branches appear reduced, while some of their homeostatic functions are compromised. This astrocytic response has been detected in several neurodegenerative and neuropsychiatric disorders (Heneka et al. 2010; Verkhratsky et al. 2014; Verkhratsky et al. 2017b). Schizophrenia, major depressive disorder, alcohol abuse disorder, and obsessive-compulsive disorders are all characterized by a reduction in the number or the packing density of astrocytes, accompanied by failure of their homeostatic function, especially in glutamate homeostasis (Aida et al. 2015; Czeh and Nagy 2018; Korbo 1999; Rajkowska et al. 2002; Rajkowska and Stockmeier 2013). Aberrant glutamate metabolism and transport, as well as the subsequent alteration in Ca^{2+} homeostasis, likely provoke an alteration in neurotransmission and excitotoxic neuronal death, both resulting in psychotic symptoms (Verkhratsky et al. 2014). Of note, Miguel-Hidalgo in his chapter published in this book offers evidence in the field of alcohol abuse disorder suggesting that the reduced number of astrocytes and the shrinkage of their processes may impair some of their critical functions. For instance, it has been shown that alcohol inhibits astrocyte proliferation, as well as DNA and protein synthesis, in cultured neonatal astrocytes (Davies and Cox 1991; Guerri and Renau-Piqueras 1997). Similar findings have also been achieved analyzing postmortem human brain tissue (Kane et al. 1996). In the chapter by Kruyer and Scofield, the emerging research highlighting the critical contribution of astrocytes to the encoding and expression of motivated behaviors relevant to drug addiction is extensively discussed. The chapter by Tanaka discusses the role of astrocytic control of the synaptic efficacy and its dysfunction in the pathophysiology of obsessive-compulsive and related disorders.

Astrocyte Pathological Remodeling in Cognitive Disorders

Astrocytes can undergo modifications in their intracellular cascade signaling or in their functional properties acquiring a pathological phenotype. This process is called pathological remodeling, and it has been implicated in the progression of several neurological diseases (Ferrer 2018; Pekny et al. 2016). Astrocytic pathological remodeling has been documented in diseases with severe damage to the developing white matter, mainly leukodystrophies. These are a group of hereditary diseases characterized by the accumulation of substances in the myelin that, therefore, gradually undergoes destruction. Alexander's disease is a rare neurodegenerative disease of astrocytes that display sporadically mutated GFAP gene that causes early and severe leukomalacia (Messing et al. 2012). Pathological remodeling in astrocytes has also been observed in other pathologies, that is, mesial

temporal lobe epilepsy and Van der Knaap disease (Bedner et al. 2015; Lanciotti et al. 2013; Verkhratsky et al. 2019).

Envoi

We concisely examined the neuroglia, the origin of these cells, their classification, and some of their functions. We have deepened the aspects connected to the homeostatic function of astrocytes, and then we tersely reviewed the modification that astrocytes undergo in neuropsychiatric diseases. In the follow-up chapters collected for this book, we explore the role of astrocytes in the progression of neuropathological diseases, particularly in neuropsychiatric disorders.

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Astrocytes: The Housekeepers and Guardians of the CNS

Alexei Verkhratsky, Vladimir Parpura, Baoman Li, and Caterina Scuderi

Astroglia: Definition and Evolutionary Origins

Astroglia represents a class of neural cells of the ectodermal, neuroepithelial origin which are the principal homeostatic cells of the central nervous system (CNS) (Verkhratsky and Nedergaard 2016, 2018). The class of astroglia includes several cellular subtypes with distinct morphology and function (Fig. 1); astroglia includes parenchymal astrocytes of several types, radial astrocytes, tanycytes, pituicytes, ependymocytes, choroid plexus cells and retinal pigment epithelial cells. The term astrocyte (αστρον κψτοσ; *astron, star and kytos, a hollow vessel,* later *cell* that is a star-like cell) was introduced by Michael von Lenhossék in 1895 (Lenhossék 1895); for the history of glial research see also (Kettenmann and Verkhratsky 2008; Chvatal

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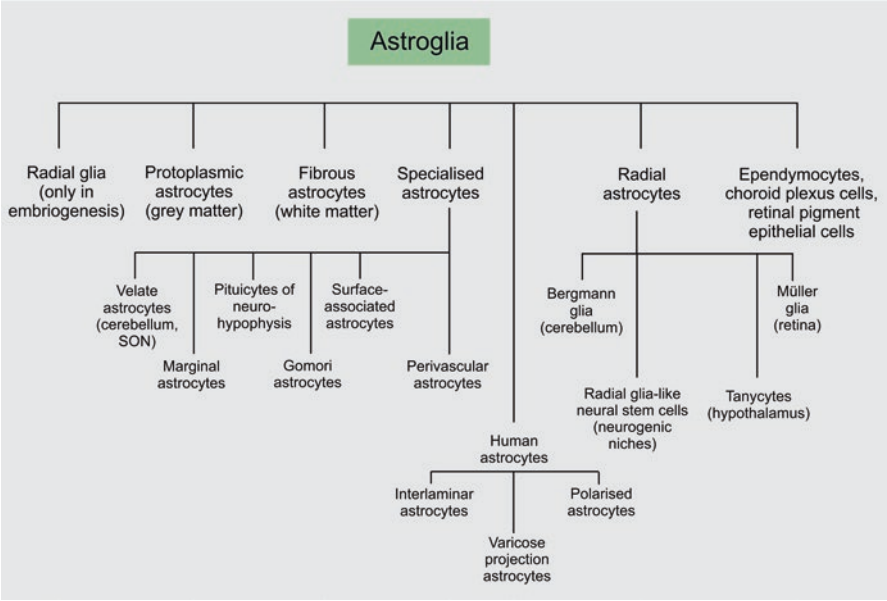

Fig. 1 Classification of astroglia

and Verkhratsky 2018). Lenhossék suggested naming all parenchymal neuroglia 'spongiocytes,' while the term astrocyte he reserved to a sub-population of cells with star-like appearance when stained with the Golgi black reaction. Parenchymal (or protoplasmic) astrocytes in the nervous tissue indeed have complex spongioform morphology defined by extensive arborisation.

Astroglial cells originate from radial glia that produce, through asymmetric division, astroglial progenitors. These progenitors populate the brain and, in the early postnatal period, propagate through symmetric division, thus producing the bulk of parenchymal astrocytes. After birth radial glial cells directly transform (transdifferentiate) into astrocytes; in neurogenic niches, these astrocytes can act as stem cells underlying adult neurogenesis.

Types of Astroglia

Protoplasmic Astrocytes

The terms of protoplasmic and fibrous glia, populating grey and white matter, respectively, have been introduced by Albert von Kölliker and William Lloyd Andriezen (Andriezen 1893; Kölliker 1896). Protoplasmic astrocytes are located in the grey matter of the brain and of the spinal cord; they have round somata of ~10μm in diameter and several primary processes. The primary processes divide into

processes of higher order; these processes host tiny terminal processes, frequently referred to as peripheral astrocytic processes (PAPs); they are presented in a form of membranous leaflets, which give protoplasmic astrocyte distinctive spongioform appearance (Bushong et al. 2002; Popov et al. 2020). Processes of protoplasmic astrocytes can also be classified into (i) branches that represent processes containing organelles and (ii) leaflets which are thin membranous structures devoid of organelles (Fig. 2); protoplasmic astrocytes extend at least one process to the nearby

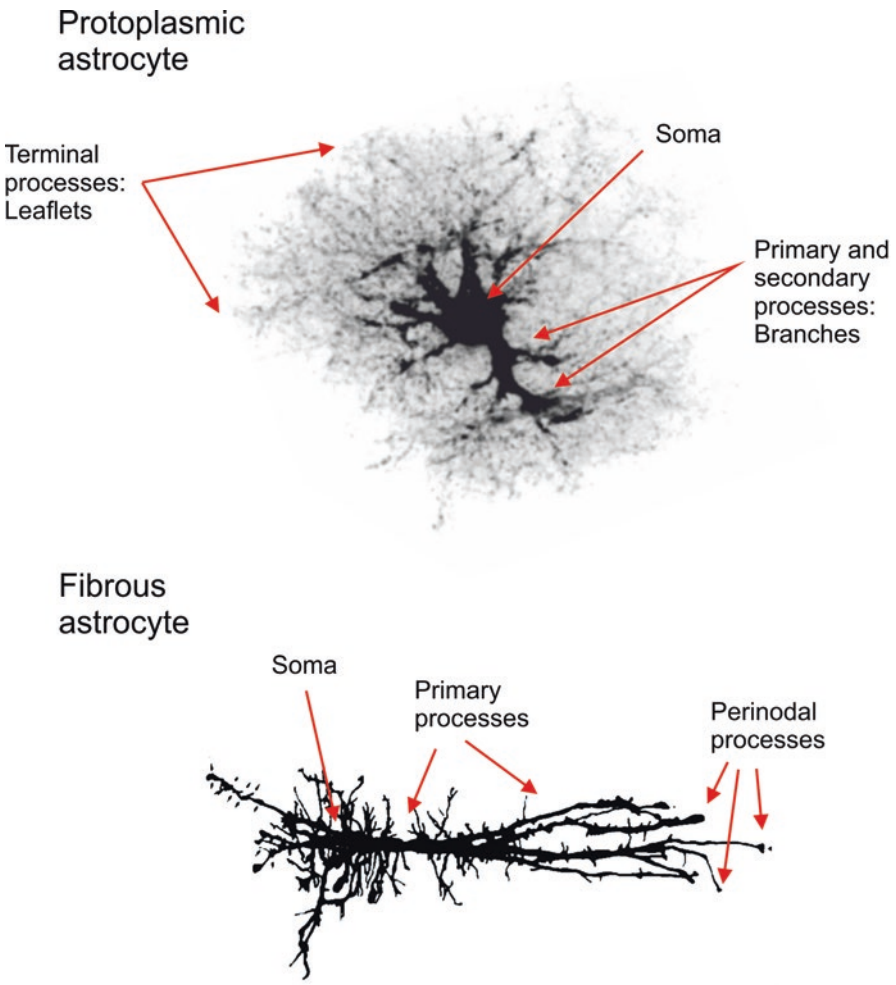

Fig. 2 Protoplasmic and fibrous astrocytes. Protoplasmic astrocytes of the grey matter are composed of soma, primary processes or branches and organelle-free thin leaflets. Fibrous astrocytes of the white matter contain perinodal processes by which they contact oligodendrocytes and nodes of Ranvier. The protoplasmic astrocyte was traced using image provided by Milos Pekny (Gothenburg University); the camera lucida image for fibrous astrocyte was provided by Arthur Butt from University of Portsmouth

blood vessel. These vascular processes end up with endfeet that cover blood vessels and form *glia limitans vascularis* (Khakh and Sofroniew 2015). Protoplasmic astrocytes occupy independent territorial domains; the neighbouring astrocytes overlap only with their distal processes and the degree of overlap does not exceed 5% (Bushong et al. 2002); this however may not occur in all species. Territories occupied by protoplasmic astrocytes define the confines of neurogliovascular units, which integrate parenchymal cellular elements with blood vessels (Iadecola 2017). Gap junctions, made from connexons and located at distal processes, integrate astrocytes into anatomically segregated syncytia (Giaume et al. 2021). The leaflets and peripheral branches contact synapses, creating a multipartite synapse or astroglial cradle that supports many aspects of synaptic function (Verkhratsky and Nedergaard 2014). Human protoplasmic astrocytes are substantially (10–20 times) larger and more complex than protoplasmic astrocytes in rodents (Oberheim et al. 2009).

Fibrous Astrocytes

Fibrous astrocytes dwell in the white matter, in the optic nerve and in the nerve fibre layer of the retina. Fibrous astrocytes (Fig. 2) have small somata and straight nonbranched processes (up to 100μm in length) oriented in parallel to axonal bundles. These processes end up with multiple finger-like cytoplasmic protrusions (perinodal processes) that are establishing contacts with axonal perinodal spaces of the surrounding axons (Lundgaard et al. 2014). Fibrous astrocytes also contact blood vessels and create perivascular or subpial endfeet. Morphology of fibrous astrocytes is heterogeneous. In rodent optic nerve, fibrous astrocytes are classified (according to morphology) into transverse, random and longitudinal (Butt et al. 1994). Human fibrous astrocytes are approximately two times larger than the same cells in rodents (Oberheim et al. 2009).

Juxtavascular Astrocytes

A sub-population of protoplasmic astrocytes located in close proximity to the blood vessels is known as juxtavascular astrocytes. These cells have some distinct physiology and demonstrate proliferative potential in response to traumatic brain injury (Bardehle et al. 2013; Gotz et al. 2021).

Surface-Associated Astrocytes

Surface-associated astrocytes are the main cellular elements of the glia limitans externa in the posterior prefrontal and amygdaloid cortex. The cell bodies of surface-associated astrocytes are located at the cortical surface, and there are two types of processes: long parallel superficial process running beneath the pia mater vessels and shorter processes extending in all directions, with some of them projecting into the cortical layer 1 (Feig and Haberly 2011).

Velate Astrocytes

Velate astrocytes represent a special population of parenchymal astrocytes covering somata of densely packed neurones in the olfactory bulb or in the granular layer of the cerebellar cortex. Velate astrocytes are characterised by a small soma with several primary processes, which form large leaflets (with high surface-to-volume ratio of 20–30μm^{-1}) enwrapping neuronal cell bodies. These perineuronal processes look like extended leaves, which defined their name derived from *vellum* (parchment in Latin) or *velatus* (which is Latin word for covered, wrapped, veiled). In the cerebellum these veil-like processes mainly cover the somata of granule cells/neurones (with a single astrocyte covering several neurones) as well as somata of Purkinje cells/neurones (Chan-Palay and Palay 1972; Buffo and Rossi 2013).

Radial Astrocytes

Radial astrocytes, named so because of their radially extended processes, are represented by (i) cerebellar Bergmann glial cells; (ii) retinal Müller glia; (iii) radial astrocytes of the supraoptic nucleus; (iv) radial glia-like neural stem cells, localised in neurogenic niches, and (v) tanycytes present in the periventricular organs, in the hypothalamus, in the hypophysis/pituitary gland and in the raphe part of the spinal cord (Reichenbach and Bringmann 2017; Verkhratsky and Nedergaard 2018).

Interlaminar and Varicose Projection Astrocytes in the Primate Brain

The brain of higher primates, and most notably of humans, contains several types of astrocytes which cannot be found in other species. These include (i) interlaminar astrocytes, with small somata located in the upper cortical layers and long processes penetrating through cortical layers; (ii) polarised astrocytes, with somata positioned

in deep cortical layers, with several long processes penetrating into superficial cortical layers, and (iii) varicose projection astrocytes characterised by several very long (up to 1 mm) unbranched processes bearing varicosities and extending in all directions through the deep cortical layers (Oberheim et al. 2009; Sosunov et al. 2014; Colombo 2017).

Physiology of Astrocytes

Astrocytes control the homeostasis of the CNS at all levels of organisation. This includes homeostasis of ions, pH and neurotransmitters; supplying neurones with metabolic substrates; supporting oligodendrocytes and axons; regulating synaptogenesis, neurogenesis, and formation and maintenance of the blood-brain barrier (BBB); contributing to operation of the glymphatic system and regulating systemic homeostasis with some astrocytes being central chemosensors for oxygen, CO_2 and Na^+ (Verkhratsky and Nedergaard 2018).

Despite substantial morphological and functional heterogeneity, all astrocytes have common basic physiological features. First and foremost, all astrocytes are electrically non-excitable cells maintaining negative resting membrane potential (V_m) of about −80 mV. This is set up by transmembrane ionic gradients and very high membrane K^+ permeability. Intracellular concentrations of major ions in astrocytes are somewhat different from neurones: in particular astrocytic cytoplasmic Na^+ concentration is around 15–20 mM (which is twice as high as in neurones), and cytoplasmic concentration of Cl^- is maintained at 30–50 mM (compare to ~5–10 mM in neurones). Intracellular concentration of Ca^{2+} in astrocytes is again higher than in the majority of neurones (~ 120–200 nM vs. 50–100 nM, respectively). Astrocytic intracellular concentration of K^+ is ~120–140 mM, which is quite similar to neuronal cytosolic K^+ (Verkhratsky and Nedergaard 2018). High membrane K^+ permeability stipulates low input resistance (5–20 MΩ) of astrocytes (Fig. 3).

Ion Channels

As mentioned above astroglial membrane permeability is dominated by K^+ channels. Astrocytes express several types of K^+ channels with distinct voltage dependence, which covers the whole range of physiological membrane potentials. As a result astrocytes demonstrate linear current-voltage relationship, which is their most characteristic electrophysiological signature maintained in vitro, in situ and in vivo (Fig. 4). This diverse complement of K^+ channels allows maintenance of hyperpolarised membrane potential, which in turn provides the electrical gradient governing numerous membrane transporters and is thus critical for astroglial homeostatic function.

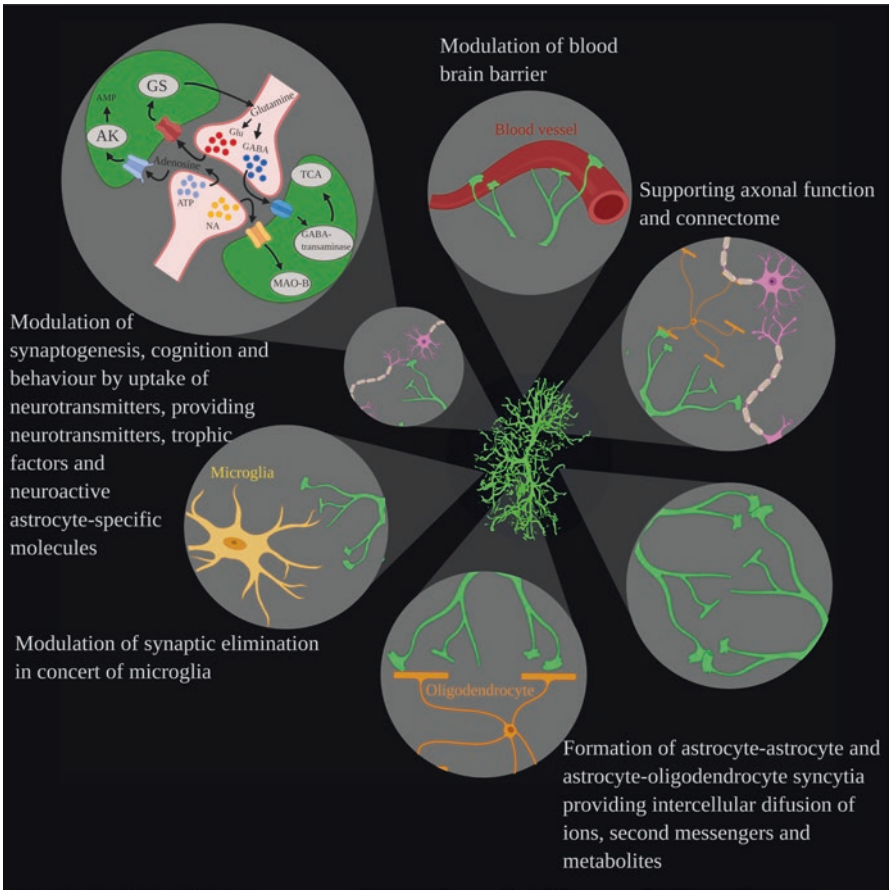

Fig. 3 Functions of astrocytes. Astrocytes interact with diverse cellular structures including blood vessels, oligodendrocytes, neurones, microglia and other astrocytes, contributing to various functions (clockwise from the top) such as regulation of the blood-brain barrier, supporting axons, myelination and connectome, forming astrocyte-astrocyte and astrocyte-oligodendrocyte syncytia, controlling (in concert with microglia) synaptic elimination and modulating synaptogenesis, cognition and behaviour by the neurochemical dialogue with synapses. (Reproduced from Augusto-Oliveira et al. (2020))

Inward rectifier potassium channels are most abundantly expressed in astrocytes. The main type of astrocytic inward rectifier channels is the $K_{ir}4.1$ subtype (encoded by *KCNJ10* gene). These $K_{ir}4.1$ channels are expressed in astrocytes throughout the brain, in the spinal cord and in the retina (Kalsi et al. 2004; Butt and Kalsi 2006). K^+ flux through $K_{ir}4.1$ channels refines the resting membrane potential of astrocytes; pharmacological suppression or genetic deletion of these channels depolarises astrocytes by ~20 mV (Olsen et al. 2007; Seifert et al. 2009). Astrocytes also express $K_{ir}5.1$ channels which may co-assemble with $K_{ir}4.1$. channels; the resulting heteromeric channels are particularly densely expressed in perisynaptic

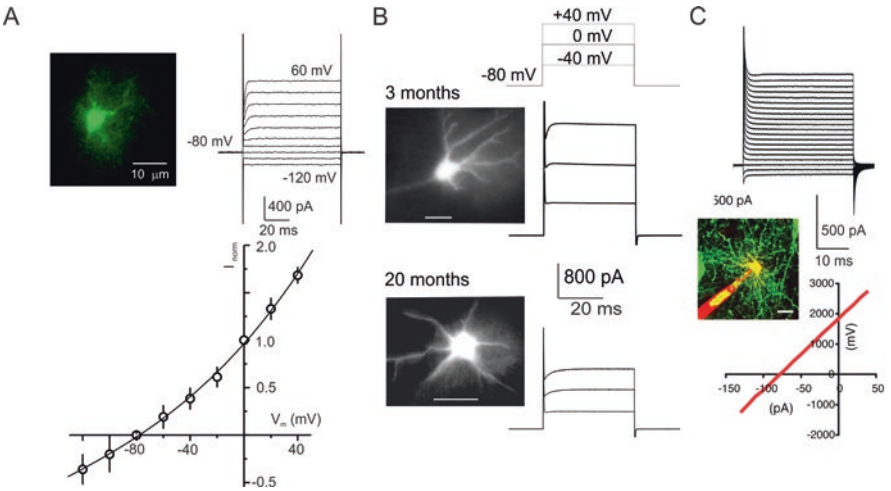

Fig. 4 Passive membrane properties of astrocytes. (**a**) Voltage-clamp recordings from astrocytes freshly isolated from the cortex of transgenic mice expressing EGFP under control of the GFAP promoter. Astrocytes were identified by specific EGFP fluorescence; whole-cell currents were recorded in response to hyper- and depolarising steps from −120 to +60 mV (step interval 20 mV). To construct the I–V relationship, amplitudes of currents were normalised to the value measured at 0 mV; every point is mean ± SD for 20 cells. (**b**) Voltage-clamp recordings from astrocytes in acute slices obtained from 3-month-old and 20-month-old *gfa*::EGFP mice; astrocytes were identified by fluorescence. (**c**) Voltage-clamp recordings from human astrocytes grafted into mouse brain. (Reproduced with permission from Verkhratsky and Nedergaard (2018))

and perivascular astroglial processes (Hibino et al. 2004; Brasko et al. 2017). The ATP-sensitive inward rectifying K^+ channels (assembled from $K_{ir}6.x$ subunit and SUR1/2) have been also detected in astrocytes; these channels are activated in conditions of intracellular ATP depletion (Eaton et al. 2002; Skatchkov et al. 2002). Resting astroglial K^+ permeability is also mediated by several voltage-independent channels of TREK and TWIK families including TREK1/K_{2P}2.1, TREK2/K_{2P}10.1 and TWIK1/K_{2P}1.1 channels (Seifert et al. 2009; Zhou et al. 2009).

In addition to inward rectifying channels, astrocytes express voltage-dependent K^+ channels, which include $K_v1.5$ (KCNA5), $K_v1.4$ (KCNA4) and $K_v11.1$/ERG1 (Bordey and Sontheimer 2000; Verkhratsky and Steinhauser 2000; Edwards et al. 2002) and K_v1, K_v3 and K_v4 mediating fast A-type K^+ currents (Bekar et al. 2005). Finally, cortical astrocytes express SK (small conductance K_{Ca} 2.3/KCNN3) and IK (intermediate conductance $K_{Ca}3.1$/KCNN4) Ca^{2+}-dependent K^+ channels in their somata (Armstrong et al. 2005; Longden et al. 2011) and large-conductance (225 pS) BK (big conductance) channels in their endfeet (Filosa et al. 2006).

Several types of other voltage-dependent channels have been identified in astrocytes. These include tetrodotoxin (TTX)-sensitive and TTX-resistant Na^+ channels which were mainly characterised in cultured astrocytes (Sontheimer et al. 1991; Sontheimer and Waxman 1992; Sontheimer et al. 1994). At transcriptional and protein levels, astrocytes were found to express mainly $Na_v1.5$ subunit, with lower

levels of $Na_v1.2$, $Na_v1.3$ and $Na_v1.6$ channels (Pappalardo et al. 2014a, 2016; Zhu et al. 2016). Similarly, astrocytes were reported (at mRNA and sometimes at protein levels) to possess voltage-gated Ca^{2+} channels mainly of $Ca_v1.2$ and $Ca_v1.3$ types (Latour et al. 2003; Cahoy et al. 2008; Zhang et al. 2014). There are only few reports for functionally active Ca^{2+} channels in astrocytes in slice preparations (Parri et al. 2001; Letellier et al. 2016) with no evidence for these channels being operative in vivo.

Astrocytes in the subfornical organ express a specific type of Na^+ channel known as Na_x (encoded by SCN7A gene). This channel is activated by an increase in extracellular Na^+ concentration above 140 mM and contribute to astroglia-dependent chemosensing of Na^+ fluctuations in circulation (Hiyama et al. 2013; Noda and Sakuta 2013). Another channel type that may be involved in Na^+ chemosensing is the epithelial Na^+ channel (ENaC). Immunoreactivity for ENaC has been found in astrocytes in circumventricular organs, white matter and pia mater (Miller and Loewy 2013).

Astrocytes are in possession of several types of transient receptor potential channels (TRP). The TRPA1 (ankyrin-type) channel is operational in the somata and processes of astrocytes in the brain stem and hippocampus; these channels provide for background Ca^{2+} entry thus regulating resting Ca^{2+} concentration in the cytoplasm (Shigetomi et al. 2012, 2013). The TRPC1 (or canonical-type)-containing channels mediate the store-operated Ca^{2+} entry following depletion of Ca^{2+} stores (Malarkey et al. 2008; Reyes et al. 2013; Verkhratsky and Parpura 2014). The TRPV1 and TRPV4 (vanilloid-type) are identified in cortical, hippocampal and spinal cord astrocytes, where they are activated in response to hypo-osmotic stress and cell swelling (Benfenati et al. 2007; Butenko et al. 2012). The store-operated Ca^{2+} entry in astrocytes is also mediated by ORAI 1 and ORAI3 channels activated by the endoplasmic reticulum (ER) Ca^{2+} sensor STIM1 (Kwon et al. 2017; Toth et al. 2019).

Astrocytes are the main type of neural cells that express water channels or aquaporins (AQP). The most abundant is AQP4, with much lesser expression of AQP1 and AQP9. In healthy conditions, the AQP4 channels are predominantly concentrated in astrocytic perivascular and pial endfeet (Nagelhus and Ottersen 2013). These channels contribute to many functions from olfaction and K^+ buffering to synaptic plasticity and memory (Lu et al. 2008; Skucas et al. 2011; Scharfman and Binder 2013; Lisjak et al. 2017). The endfeet AQP4 channels are particularly important for the function of the glymphatic system (Mestre et al. 2020).

Astrocytes are functionally integrated into syncytia by gap junctional plaques which are composed of several hundred of intercellular channels known as connexons, with each connexon being assembled from 12 subunits known as connexins (Giaume et al. 2021). Astrocytes express three types of connexins, namely, Cx26, Cx30 and Cx43, of which Cx43 is the most abundant and most widespread being expressed in all CNS regions (Nagy et al. 2004). Connexons assembled from Cx30 are mainly present in the thalamus and leptomeninges (Nagy et al. 2004; Sohl et al. 2004), whereas Cx26 is confined to the hypothalamus, reticular thalamic and subtalamic nuclei (Nagy et al. 2011). Astrocytes also establish

syncytial connections with oligodendrocytes; the astrocyte-oligodendrocyte connexons are assembled from heterotypic channels composed of Cx47/Cx43, Cx32/Cx30, Cx47/Cx30 or Cx32/Cx26, of which the first two are predominant types in vivo (Orthmann-Murphy et al. 2007; Magnotti et al. 2011). Unpaired connexons, also known as hemichannels, have been identified in astrocytes in various brain regions, and they may mediate (together with Pannexin channels) diffusional secretion of various neuroactive substances (Orellana et al. 2009; Giaume et al. 2013; Verkhratsky et al. 2016).

Receptors of Neurotransmitters

Fundamentally, astrocytes are capable of expressing virtually every type of neurotransmitter/neuromodulator receptor existing in the CNS. At the same time this potential promiscuity is very much restricted by the neurochemical environment in different parts of the CNS. Generally, astrocytes express receptors of the same modality as their neuronal neighbours; these modalities are congruent to the neurotransmitters released in a given brain region (Verkhratsky et al. 1998; Verkhratsky 2010). For example, in the spinal cord, where glycine is the main inhibitory neurotransmitter, astrocytes specifically express glycine receptors; in the basal ganglia, which utilise dopamine, astrocytes are endowed with dopamine receptors. Thus, the expression of astroglial receptors in vivo is regulated by neurochemical input, which makes astrocytes perceptive to regional neurochemical environment.

Probably the most abundant astrocytic receptors are receptors of purines, as the purinergic signalling system is omnipresent in the CNS (Burnstock and Verkhratsky 2012). Metabotropic purinoceptors, represented by ATP/ADP $P2Y_{1,2,4,6,12,13}$ and UDP-glucose $P2Y_{14}$ receptor, predominate (Abbracchio and Ceruti 2006; Verkhratsky et al. 2009). Activation of metabotropic P2Y receptors is linked, through phospholipase C (PLC) and inositol-1,4,5-trisphophate ($InsP_3$) receptors to Ca^{2+} signalling. Astrocytes also possess ionotropic purinoceptors, mainly of $P2X_7$ type; murine cortical astrocytes also have $P2X_{1/5}$ receptors (Lalo et al. 2008, 2011; Illes et al. 2012). Activation of ionotropic purinoceptors contributes to both Ca^{2+} and Na^+ signalling in astrocytes.

The second class of astrocytic neurotransmitter receptors is represented by receptors of amino acid glutamate, GABA and glycine. Again astrocytes express several types of glutamate receptors. Ionotropic glutamate receptors functionally expressed in astrocytes are represented by AMPA receptors (with all four subunits being expressed, albeit in brain region-dependent fashion) and NMDA receptors. The latter are composed of two GluN1 subunits assembled with GluN2C or D and GluN3 subunits. Such composition infers weak Mg^{2+} block (which develops at ~ −120 mV) and relatively low Ca^{2+} permeability ($P_{Ca}/P_{monovalent}$ ~ 3), as well as sensitivity to memantine and GluN2C/D subunit-selective antagonist UBP141 (Lalo et al. 2006; Palygin et al. 2010; Verkhratsky and Chvatal 2020). Astrocytes also express

metabotropic glutamate receptors, of which mGluR3 (connected to cAMP signalling cascade) and $mGuR_{1/5}$ (connected to PLC-$InsP_3$-Ca^{2+} signalling cascade) predominate. Astrocytes express ionotropic $GABA_A$ receptors, which mediate Cl^- currents and, because of high $[Cl^-]i$, depolarise the membrane (Kettenmann et al. 1987); astrocytic metabotropic $GABA_B$ receptors are linked to PLC-$InsP_3$-Ca^{2+} signalling cascade (Nilsson et al. 1993). Spinal cord astrocytes express glycine receptors which mediate Cl^- efflux and astrocytic depolarisation (Pastor et al. 1995).

The third class of receptors abundantly present in astrocytes is represented by receptors for monoamines. In particular, most of astrocytes express α- and β-adrenoceptors that were detected in culture, in slices and in vivo at transcriptional, protein and functional levels (Verkhratsky and Nedergaard 2018). Both α_1 and α_2 adrenoceptors are linked to Ca^{2+} signalling (Kirischuk et al. 1996; Ding et al. 2013); β_1-adrenoceptors regulate glycogen synthesis, β_2-adrenoceptors are linked to cAMP signalling and β_3-adrenoceptors regulate glucose uptake by modulating GLUT1 plasmalemmal glucose transporter (Hutchinson et al. 2007; Dong et al. 2012). In addition, astrocytes express 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B} and 5-HT_{5A} metabotropic serotonin receptors, as well as D_1, D_2, D_4 and D_5 dopamine receptors, and H_1, H_2 and H_3 histamine receptors (Verkhratsky and Nedergaard 2018).

Other receptors expressed in astrocytes include B_2 bradykinin receptors, cannabinoid CB_1 receptors, V_1 vasopressin receptors, oxytocin receptors, ET_A and ET_B endothelin receptors, atrial natriuretic peptide receptors, receptors for leptin and insulin, platelet-activating factor receptors and protease-activated receptors, which fulfil various functions and are linked to different signalling cascades (Verkhratsky and Nedergaard 2018).

Astroglial Plasma Membrane Transporters

Plasmalemmal transporters are fundamentally important for astroglial homeostatic function because they accomplish transport of ions, neurotransmitters, scavengers of reactive oxygen species (ROS), metabolic substrates and various neuromodulators and hormones. All plasmalemmal transporters are classified into pumps (which utilise energy of ATP) and secondary plasmalemmal transporters or solute carriers (SLC) which use concentration gradients.

Astroglial Na^+-K^+ pump (NKA) has the idiosyncratic α2 catalytic subunit, which distinguishes it from the neuronal NKA, which contains α1 or α3 subunits. The affinity of the astroglial α2 subunit to extracellular K^+ is much lower as compared to neuronal α1 and α3 subunits: $[K^+]_{0.5}$ for NKA composed from α2/β1 subunits is ~3.6 mM, whereas $[K^+]_{0.5}$ for neuronal NKAs assembled from α1/β1, α1/β2, α3/β1 or α3/β2 subunits lies between 0.25 and 0.65 mM (Larsen et al. 2014). As consequence, the activity of astroglial NKA is stimulated by physiological increases in the extracellular K^+ concentration. To the contrary neuronal NKA is fully saturated and hence cannot respond to increases in extracellular K^+ (Hertz et al. 2015). This

stipulates the leading role of NKA in astrocytic K^+ buffering (Verkhratsky and Nedergaard 2018).

Astrocytic SLC transporters are many and they perform numerous homeostatic functions. The largest group of homeostatic SLC transporters is represented by transporters for neurotransmitters; the majority of these transporters utilise transmembrane Na^+ gradient to move neurotransmitters across the plasma membrane. Astrocytic transporters for glutamate are known as excitatory amino acid transporters 1 and 2 (EAAT1/SLC1A6 and EAAT2/SLC1A2 (Zhou and Danbolt 2013)), which in rodent experiments are referred to as glutamate-aspartate transporter (GLAST (Storck et al. 1992)) and glutamate transporter 1 (GLT-1 (Pines et al. 1992)). EAAT1 is mainly present in the cerebellum, in the retina and in circumventricular organs, whereas EAAT2 is expressed in all other parts of the brain; at the cellular level both transporters localise to perisynaptic astroglial processes (Zhou and Danbolt 2013; Verkhratsky and Nedergaard 2018). Glutamate transporters are Na^+-dependent with stoichiometry 3 Na^+, 1 H^+ and 1 glutamate (in): 1 K^+ (out) (Zerangue and Kavanaugh 1996). This transporter is electrogenic and generates transmembrane current carried mainly by Na^+ ions (Kirischuk et al. 2007). In addition to EAATs, astrocytes express the cystine/glutamate antiporter Sxc^- (SLC7A11) which is critical for cystine accumulation needed for the production of glutathione (Bridges et al. 2012). Glutamate homeostasis also depends on astrocytic glutamine transporters SNAT3/SLC38A3 and SNAT5/SLC38A5 which couple transport of glutamine with co-transport of 1 Na^+ and counter-transport of 1 H^+ (Todd et al. 2017). Astroglial GABA transporters are mainly represented by GAT3/SLC6A11 with stoichiometry of 1 GABA: 2 Na^+: 1 Cl^- (Kavanaugh et al. 1992); moderate increases in cytoplasmic Na^+ may reverse this transporter (Unichenko et al. 2012). Astrocytes in the spinal cord possess glycine transporter GlyT1/SLC6A9 with stoichiometry of 1 glycine: 2 Na^+: 1 Cl^-; this transporter also can reverse in physiological conditions (Shibasaki et al. 2017). Monoamine accumulation into astrocytes is mediated by norepinephrine transporter NET/SLC6A2 that co-transports monoamines with 2 Na^+ and 1 Cl^- (Takeda et al. 2002). Astrocytes transport adenosine by equilibrative (i.e. controlled by adenosine transmembrane gradient (King et al. 2006)) plasmalemmal transporters ENT-1/SLC29A1, ENT-2/SLC29A2, ENT-3/SLC29A3 and ENT-4/SLC29A4, and Na^+-dependent concentrative nucleoside plasmalemmal transporters CNT2/SLC28A2 and CNT3/SLC28A3 (King et al. 2006; Li et al. 2013).

The next group of SLC transporters is responsible for ion exchange. The most prominent member of this group is plasmalemmal sodium-calcium exchanger present in astrocytes in three isoforms NCX1/SLC8A1, NCX2/SLC8A2 and NCX3/SLC8A3 (Pappalardo et al. 2014b). Stoichiometry of astrocytic NCX is 3 Na^+: 1 Ca^{2+} which sets the equilibrium potential at ~ −85 to −90 mV; this is very close to the resting membrane potential of astrocytes, and hence minor depolarisations or moderate increases in cytosolic Na^+ readily reverse NCX operation from the forward mode (extrusion of Ca^{2+} in exchange for Na^+) to the reverse mode (Ca^{2+} influx in exchange for Na^+ exit) (Verkhratsky et al. 2018). Another transporter expressed in astrocytes is the NHE1/SLC9A1 Na^+-H^+ exchanger (Deitmer and Rose 1996;

Chesler 2003) with electroneutral stoichiometry of 1 Na^+ (in): 1 H^+ (out) (Orlowski and Grinstein 1997); this transporter mediates efflux of protons from astrocytes (Rose and Ransom 1996; Chesler 2003). Additional transporter involved in pH homeostasis is the sodium-bicarbonate transporter NBCe1/SLC4A4 with stoichiometry of 1 Na^+: 2 HCO_3^- or 1 Na^+: 3 HCO_3^-, which allows its operation in both forward and reverse modes (Theparambil et al. 2015). The Na^+-K^+-Cl^- co-transporter NKCC1/SLC12A2 with electroneutral stoichiometry of 1 Na^+: 1 K^+: 2 Cl^- contributes to K^+ and Cl^- homeostasis especially in pathology (Macaulay and Zeuthen 2012).

Finally, astrocytes express several metabolic transporters responsible for transmembrane movements of energy substrates. In particular, astrocytes possess glucose transporter GLUT1/SLC2A1 predominantly localised in endfeet (Allen and Messier 2013). Monocarboxylate transporters 1 and 4 (MCT1/SLC16A1, MCT4/SLC16A3) are responsible for the export of lactate from astrocytes for local energy support of neurones; in certain conditions, however, these transporters can mediate lactate accumulation (Halestrap 2012).

Intracellular Excitability of Astrocytes

Astrocytes (similarly to other neuroglia) are electrically non-excitable cells of the CNS; in contrast to neurones astrocytes do not generate regenerative and propagating action potentials. At the same time astrocytes do generate active responses to all changes in nervous tissue environment; these responses are linked to transient fluctuations in cellular ionic content or generation/degradation of intracellular messengers. These molecular changes are the substrate for astrocytic excitability.

Astrocyte Ca^{2+} Excitability

Calcium ions are universal and evolutionary conserved intracellular messengers, involved in the regulation of numerous cellular processes, such as excitation-contraction coupling, secretion, gene expression, metabolism and cell death (Berridge et al. 2000; Carafoli 2002; Petersen et al. 2005; Plattner and Verkhratsky 2015). Cellular Ca^{2+} signalling and homeostatic control over cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$) rely on dedicated molecules, which include membrane channels and transporters, intracellular Ca^{2+}-binding proteins and numerous Ca^{2+} sensors represented by Ca^{2+}-regulated proteins.

Astrocytic Ca^{2+} excitability was discovered in experiments in vitro which demonstrated that challenging cultured astrocytes with neurotransmitters and neurohormones triggered $[Ca^{2+}]_i$ transients and propagating Ca^{2+} waves (Enkvist et al. 1989; Cornell-Bell et al. 1990; McCarthy and Salm 1991; Verkhratsky and Kettenmann 1996; Petersen et al. 2005). Molecular pathways underlying astrocytic Ca^{2+}

excitability rely on both intracellular and extracellular Ca^{2+} sources. Generation of Ca^{2+} signals in the soma and primary processes mainly depends on metabotropic receptors, which activate PLC that produces InsP*3*, which in turn activates $InsP_3$ receptors residing in the membrane of the ER. This organelle is the main Ca^{2+} storage organelle in living cells; it is capable of accumulating, storing and releasing Ca^{2+} in physiological context. Concentration of ionised Ca^{2+} in the lumen of the ER is rather high, ranging between 200μM and 1 mM (Alonso et al. 1999; Alvarez and Montero 2002; Solovyova and Verkhratsky 2002; Solovyova et al. 2002). High intraluminal [Ca^{2+}] creates a gradient aimed at the cellular cytosol; hence opening of Ca^{2+} release channels dwelling in the endomembrane generates Ca^{2+} efflux and thus generates cytosolic Ca^{2+} signals; in addition, intraluminal Ca^{2+} regulates both Ca^{2+} pump (SERCA, SarcoEndoplasmic Reticulum Ca^{2+}-ATPase) and Ca^{2+} release channels (Burdakov et al. 2005). Besides being a dynamic Ca^{2+} store, the ER is responsible for protein synthesis, folding and haulage to their respective destinations, with all these processes being regulated by luminal [Ca^{2+}] (Verkhratsky and Petersen 2002). Finally, the ER creates intracellular Ca^{2+} tunnels which allow long-distance diffusion of Ca^{2+}, which is impossible in heavy Ca^{2+}-buffered cytosol (Petersen and Verkhratsky 2007).

Both classes of intracellular Ca^{2+} release channels, the $InsP_3$ receptors and ryanodine receptors (which are Ca^{2+}-gated Ca^{2+}channels) are expressed in glial cells (Verkhratsky et al. 1998). In astrocytes the type II $InsP_3$ receptors predominate; these receptors are activated by InsP*3* and positively modulated by $[Ca^{2+}]_i$; local increases in $[Ca^{2+}]_i$ therefore can generate propagating wave of opening of $InsP_3$ receptors along the ER membrane, making the latter an excitable media sustaining propagating Ca^{2+} waves (Verkhratsky et al. 2012).

As alluded before, release of Ca^{2+} from the ER, mediated by $InsP_3$ receptors, represents the leading mechanism for Ca^{2+} signal generation in the soma and organelle-bearing processes; depletion of ER Ca^{2+} store activates secondary Ca^{2+} influx through plasmalemmal store-operated pathway mediated by TRP and ORAI channels (Burnstock and Verkhratsky 2012). |Generation of Ca^{2+} signals in the distal leaflets is different as it mainly relies on plasmalemmal Ca^{2+} entry (Fig. 5). The principal route for Ca^{2+} entry in response to neuronal activity is associated with the reversal of Na^+-Ca^{2+} exchanger (NCX). The latter is controlled by transmembrane Na^+ gradient; increase in $[Na^+]_i$ associated with operation of glutamate transporters reverses the NCX (Reyes et al. 2012; Rose et al. 2020). In addition, Ca^{2+} entry into the leaflets is mediated by ionotropic receptors and possibly by TRP channels (Verkhratsky et al. 2012). Such a dichotomy is characteristic for protoplasmic astrocytes; in radial Bergmann glial cells, the main mechanism for Ca^{2+} signal generation is represented by PLC-$InsP_3$ pathway (Kirischuk et al. 1999). The complex molecular machinery responsible for Ca^{2+} signalling in astrocytes results in emergence of spatially and temporally distinct Ca^{2+} signals in the form of microdomains or propagating Ca^{2+} waves of global Ca^{2+} signals (Grosche et al. 1999; Shigetomi et al. 2013; Khakh and Sofroniew 2015; Arizono et al. 2020).

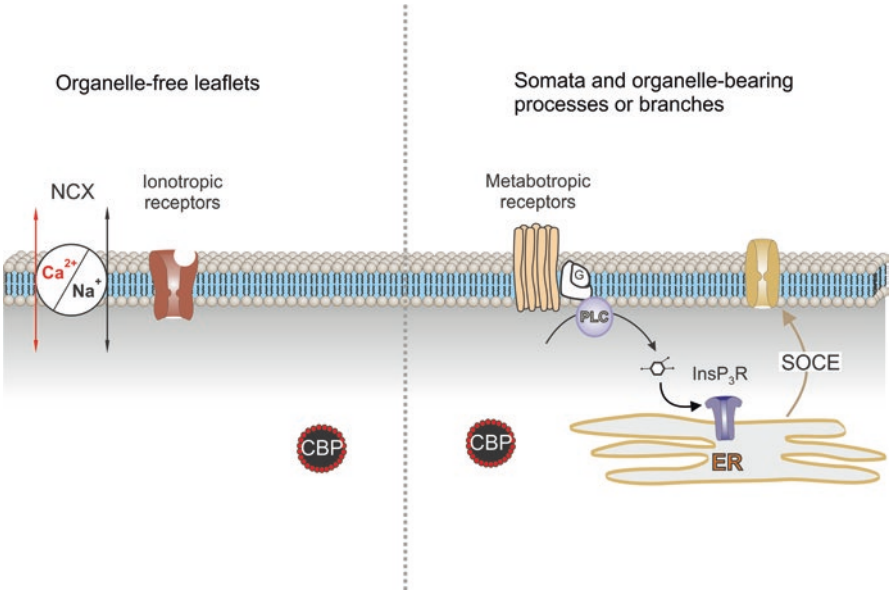

Fig. 5 Ca^{2+} signalling in different compartments in protoplasmic astrocyte. Calcium signalling in the organelle-free leaflets is associated with Ca^{2+} entry through ionotropic receptors (NMDA glutamate receptors or P2X purinoceptors) or Ca^{2+}-permeable channels (e.g. TRPA1 channels). Plasmalemmal Ca^{2+} influx can also be mediated by the Na^+/Ca^{2+} exchanger (NCX) operating in the reverse mode. Calcium signalling in soma and branches is mainly associated with Ca^{2+} release from the endoplasmic reticulum (ER) with subsequent store-operated Ca^{2+} entry (SOCE). This Ca^{2+} release is mediated by $InsP_3$ receptors ($InsP_3R$); $InsP_3$ is synthesised by phospholipase C (PLC) linked to G-protein metabotropic receptors. CBP, calcium binding proteins. (Reproduced with permission from Verkhratsky et al. (2020))

Sodium Signalling

The foundations for astrocytic Na^+ signalling are associated solely with Na^+ entry mediated by various proteins in the plasma membrane (Fig. 6). Cells have neither intracellular Na^+ stores nor cytosolic Na^+ buffers (Kirischuk et al. 2012; Rose and Verkhratsky 2016). Physiological stimulation triggers $[Na^+]_i$ transients in astrocytes in vitro and in situ (Rose and Ransom 1996; Kirischuk et al. 1997; Langer and Rose 2009). The main source for generation of Na^+ signals is mediated by Na^+ entry through Na^+-coupled SLC transporters, whereas extrusion of Na^+ is primarily mediated by NKA (Rose and Verkhratsky 2016). In addition, Na^+ influx can be mediated by ionotropic receptors and plasmalemmal channels, in particular TRPC channels (Reyes et al. 2013). Among Na^+-dependent SLC transporters, glutamate and GABA transporters play the leading role in generation of Na^+ signals. Increase in extracellular glutamate associated with neurotransmission is followed by rapid accumulation of glutamate into astrocytes; translocation of a single glutamate molecule is coupled with entry of 3 Na^+. Increase in cytosolic Na^+ concentration

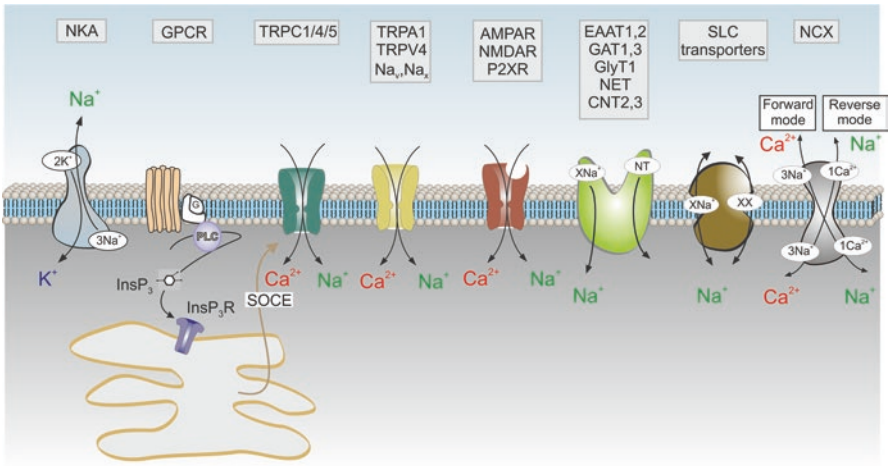

Fig. 6 Membrane molecular pathways of Na^+ signalling in astrocytes. Influx of Na^+ occurs though (i) Na^+-permeable channels which include ionotropic receptors (AMPAR, NMDAR, P2XR: AMPA, NMDA glutamate receptors and ionotropic purinoceptors, respectively); channels of the transient receptor potential (TRP) family (TRPC1/4/5 channels that operate as a part of store-operated Ca^{2+} entry and hence generate Na^+ influx in response to the depletion of endoplasmic reticulum Ca^{2+} stores; as well as TRPA1 and TRPV4 channels); voltage-dependent Na_v channels and $[Na^+]_o$-activated Na_x channels; (ii) through Na^+-dependent SLC transporters that include excitatory amino acid transporters EAAT1,2, GABA transporters GAT 1,3, glycine transporters GlyT, noradrenaline transporters NET and concentrative adenosine transporters CNT2,3. The main pathway for Na^+ exit is provided by Na^+-K^+ pump, NKA. The Na^+-Ca^{2+} exchanger NCX fluctuates between forward and reverse modes and couples Na^+ and Ca^{2+} signalling. Other abbreivations as in Fig. 5. (Reproduced with permission from Verkhratsky et al. (2020))

($[Na^+]_i$) in response to glutamate may reach 10–20 mM (Kirischuk et al. 2007; Bennay et al. 2008). The main physiological target of astroglial Na^+ signals is represented by SLC transporters sensitive to transmembrane Na^+ gradients (Fig. 7); in addition $[Na^+]_i$ regulates glutamine-glutamate (GABA) shuttle through direct action on glutamine synthetase and regulation of glutamine transporters (Benjamin 1987; Todd et al. 2017).

Astrocyte Functions

Astrocytes perform every known housekeeping and homeostatic function in the CNS from structural support and control over molecular homeostasis to regulation of blood flow, synaptogenesis, neurogenesis and development of the nervous system.

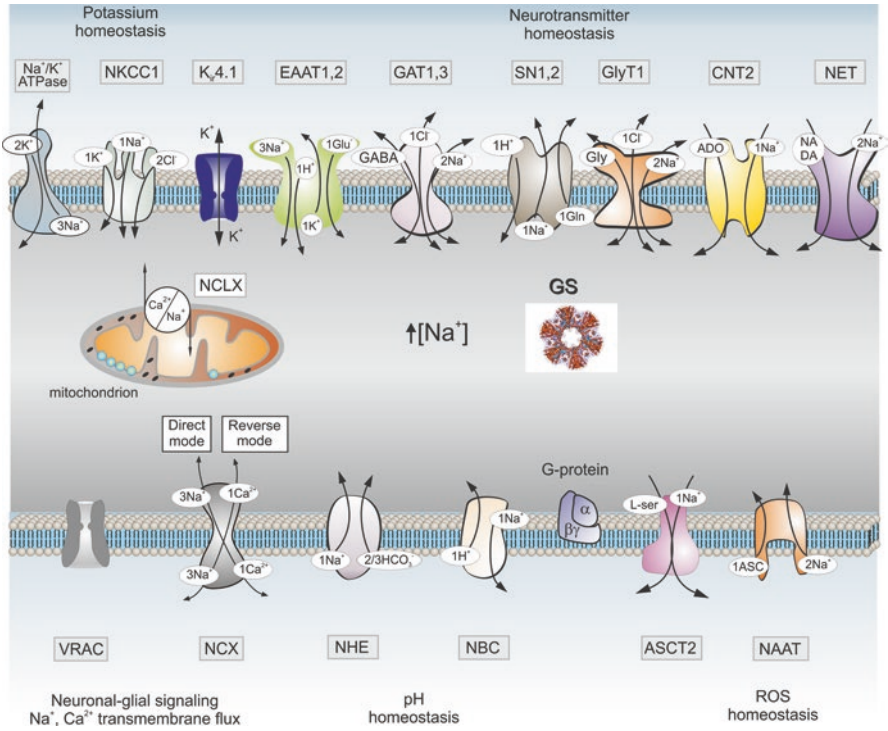

Fig. 7 Molecular targets of Na^+ signalling in astroglia. Abbreviations: ASCT2 alanine-serine-cysteine transporter 2, ASIC acid sensing ion channels, CNT2 concentrative nucleoside transporters, EAAT excitatory amino acid transporters, ENaC epithelial sodium channels, GAT GABA transporters, GS glutamine synthetase, GlyT1 glycine transporter, iGluRs ionotropic glutamate receptors, Na_x Na^+ channels activated by extracellular Na^+, NAAT Na^+-dependent ascorbic acid transporter, NBC Na^+/HCO_3^- (sodium-bicarbonate) co-transporter, NCX Na^+/Ca^{2+} exchanger, NCLX mitochondrial Na^+/Ca^{2+} exchanger, NHE Na^+/H^+ exchanger, NKCC1 $Na^+/K^+/Cl^-$ co-transporter, NET norepinephrine transporter, MCT1 monocarboxylase transporter 1, P2XRs ionotropic purinoceptors, SN1/2 sodium-coupled neutral amino acid transporters which underlie exit of glutamine, TRP transient receptor potential channels, ROS reactive oxygen species, VRAC volume-regulated anion channels. Other abbreviations as in Fig. 5. See text for further explanation. (Modified and reproduced from Verkhratsky and Nedergaard (2018))

Ion Homeostasis in the CNS, or Ionostasis

Controlling ion concentrations in the interstitial fluids is of paramount importance for the functional activity of the nervous tissue, as even minor fluctuation in ionic composition may have profound influences on neuronal excitability and information processing in the neuronal networks. In particular, changes in ion concentrations are linked to changes in the brain state, such as sleep and arousal (Ding et al. 2016), while fluctuations in ion composition of interstitial fluids affect learning and

memory (Hertz and Chen 2016). Control over ionostasis is one of the most fundamental functions of astrocytes.

Astrocytes are central for regulation of extracellular K^+ concentration, the latter being directly linked to neuronal activity and neuronal excitability. Neuronal firing and synaptic transmission are associated with substantial K^+ efflux, which may significantly change K^+ concentration in the narrow and diffusion-restricted extracellular compartments. The leading role of astrocytes in the regulation of extracellular K^+ homeostasis has been proposed in the mid-1960s by Leif Hertz, Steven Kuffler and Richard Orkand (Hertz 1965; Kuffler and Nicholls 1966; Orkand et al. 1966). Astrocytic K^+ clearance from the interstitial fluid is mainly accomplished by active transport by NKA (Larsen et al. 2014), as astrocytic NKA is directly activated by K^+ rise (see above). After being taken up by astrocytes, K^+ is subsequently released by $K_{ir}4.1$ channels back into the extracellular space, from which it is taken up by neurones to restore ionic gradients (Hertz and Chen 2016; Larsen et al. 2016). Such scenario implies the generation of K^+ microdomains, which might be supported by physical properties of bilipid membranes trapping ions in narrow compartments of astrocytic leaflets (Breslin et al. 2018). In Müller glial cells in the retina, K^+ buffering is mainly accomplished by K^+ entry through $K_{ir}4.1$ channels localised in perisynaptic processes in the inner plexiform layer of the retina. Subsequently, K^+ is spred through the cell and is released (again through $K_{ir}4.1$ channels) from the endfoot distantly to the site of accumulation; this process is known as K^+ siphoning (Newman et al. 1984; Kofuji and Newman 2004).

Another important extracellular ion that may fluctuate during neuronal activity and synaptic transmission is Ca^{2+}. Opening of plasmallemal Ca^{2+} channels with subsequent Ca^{2+} influx into presynaptic boutons may result in substantial drop in Ca^{2+} concentration in the narrow synaptic cleft, thus affecting neurotransmitter release (Rusakov and Fine 2003). Astrocytes seem to provide a pathway for replenishment of extracellular Ca^{2+} as decrease in $[Ca^{2+}]_o$ below ~0.5 mM induces $InsP_3$-induced Ca^{2+} release from the ER in astrocytes (Zanotti and Charles 1997). This Ca^{2+} then can be transported to extracellular space through plasmalemmal Ca^{2+} pumps or NCX.

A similar situation may also happen with extracellular Cl^-. Overstimulation of neuronal ionotropic $GABA_A$ receptors may result in substantial Cl^- accumulation into neurones; reduction in extracellular Cl^- concentration may subsequently impair inhibitory transmission. As astrocytes have high cytoplasmic Cl^- concentration, activation of astrocytic ionotropic $GABA_A$ receptors may initiate substantial Cl^- efflux, thus restoring extracellular Cl^- concentration (Kettenmann and Verkhratsky 2008). Indeed, manipulations with astrocytic intracellular Cl^- were demonstrated to affect inhibitory transmission in hippocampal slices (Egawa et al. 2013). Astrocytes are also principal players in regulation of extracellular pH through transport of H^+ and HCO_3^- (Deitmer and Rose 2010).

Neurotransmitter Homeostasis

Astrocytes control neurotransmitter homeostasis in the brain through removal (by dedicated transporters) and inactivation (by enzymatic conversion) of all four major neurotransmitters, namely, glutamate, GABA, adenosine and noradrenaline (Fig. 8).

Astrocytic glutamate homeostatic system is an indispensable element for glutamatergic and GABAergic transmission because it provides for (i) clearance of glutamate and GABA from the synaptic cleft, (ii) prevention of glutamate spillover and (iii) replenishment of the glutamate and GABA releasable pools of vesicles in the neuronal terminals by providing the obligatory precursor glutamine (Hertz et al. 1999; Verkhratsky and Nedergaard 2018). Astrocytic glutamate clearance also protects nervous tissue against glutamate excitotoxicity.

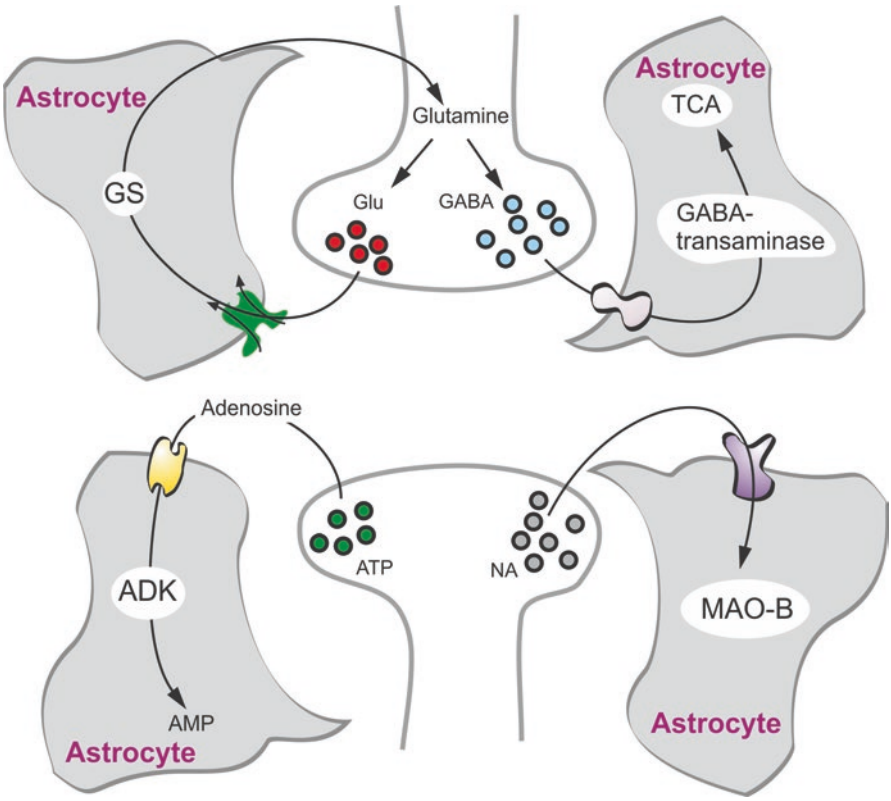

Fig. 8 Astrocytes and neurotransmitter homeostasis. Astrocytes take up glutamate, GABA, adenosine and monoamines. Glutamate (Glu) is converted to glutamine by glutamine synthetase (GS) in astrocytes which also synthesise this transmitter de novo. In turn, glutamine is shuttled to neurones for subsequent conversion into glutamate and GABA. Astroglial accumulated GABA is mainly transaminated and consumed in tricarboxylic acid cycle (TCA). Adenosine is converted to AMP by adenosine kinase (ADK), while monoamines are degraded by astroglial monoamine oxidase type B (MAO-B). (Modified and reproduced from Verkhratsky and Nedergaard (2018))

Neurones do not have enzymes for de novo synthesis of glutamate from pyruvate (generated from glucose or lactate); this synthesis occurs solely in astrocytes (Hertz et al. 1999). Glutamate produced in astrocytes is converted, with another astrocyte-specific enzyme, glutamine synthetase, into biologically inert glutamine, which is subsequently transported to neurones; when in neurones glutamine is converted into glutamate by glutaminase. In inhibitory terminals, glutamate is further converted into GABA.

Astrocytic glutamate transporters EAAT1/2 are responsible for the clearance of ~80% of all glutamate released during synaptic transmission (Danbolt 2001). Removal of glutamate by astrocytes dynamically modulates glutamate concentration in the synaptic cleft thus shaping kinetics of neuronal postsynaptic excitatory potentials (Marcaggi and Attwell 2004; Tzingounis and Wadiche 2007). Glutamate entering into astrocytes can undergo conversion to glutamine, which is subsequently shuttled to neurones through Na^+-dependent glutamine transporters (described in a previous section). Increase in $[Na^+]_i$ resulting from EAAT1/2-mediated uptake of glutamate stimulates glutamine efflux (Todd et al. 2017). This sequence of plasmalemmal transporting and enzymatic conversion is known as the glutamine-glutamate (GABA) shuttle that is fundamental for sustaining both excitatory and inhibitory neurotransmission in the CNS (Hertz 2013).

Astrocytes provide substantial contribution to the catabolism of monoamines in the CNS. The main converting enzyme that catabolises noradrenalin (norepinephrine), dopamine and serotonin, the monoamine oxidase B (MAO A/B), is preferentially expressed in astrocytes (Saura et al. 1992; Hertz et al. 2004). Monoamines are accumulated into astrocytes through plasmalemmal Na^+-dependent norepinephrine transporter NET/SLC6A2 and possibly by dopamine transporter DAT/SLC6A3 (Verkhratsky and Nedergaard 2018). Finally, astrocytes express high levels of adenosine kinase which catalyses the bulk of adenosine conversion into AMP (Boison 2008); genetic deletion of adenosine kinase is incompatible with life (Boison et al. 2010).

Astroglial Cradle in Regulation of Synaptic Transmission

Astrocytic processes, including branches and leaflets, establish intimate dynamic contacts with synaptic structures; at least 50–60% of all synaptic contacts in the CNS are covered with astrocytic membranes (Witcher et al. 2007; Reichenbach et al. 2010). These astrocytic perisynaptic structures play most fundamental role in synaptic connectivity being involved in the regulation of synaptogenesis, synaptic maturation, synaptic maintenance, synaptic isolation and synaptic extinction; this multitude of functions stipulated the emergence of the concept of astroglial cradle (Nedergaard and Verkhratsky 2012; Verkhratsky and Nedergaard 2014) (Fig. 9). Astrocytes express numerous specific pathways through which they can regulate various aspects of synaptic transmission (Augusto-Oliveira et al. 2020).

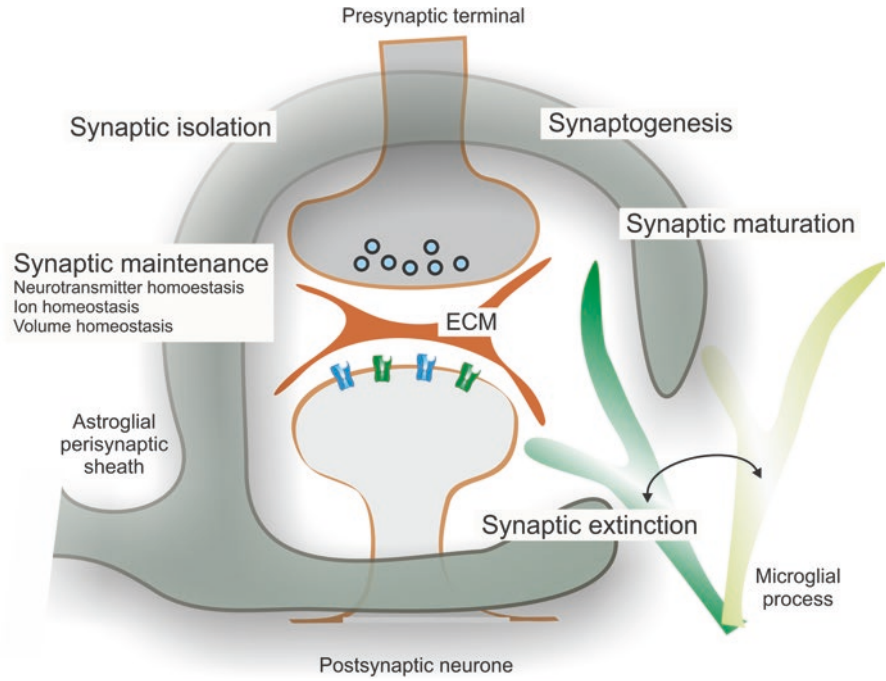

Fig. 9 Astrocytic synaptic cradle. Astroglial cradle embraces and fosters multipartite synapse in the CNS. The majority of synapses in the brain and in the spinal cord is composed of several components that include the presynaptic terminal. These components are: the postsynaptic part, the perisynaptic process of the astrocyte, the process of neighbouring microglial cell that periodically contacts the synaptic structure and the extracellular matrix (ECM) present in the synaptic cleft and also extending extra-synaptically. Astroglial perisynaptic sheath enwraps synaptic structures; regulates, influences and assists synaptogenesis, synaptic maturation, synaptic maintenance and synaptic extinction; and also modulates synaptic transmission and plasticity. (Reproduced from Verkhratsky and Nedergaard (2014))

Synaptogenesis in particular requires astrocytes and astrocytic factors. The massive emergence of excitatory glutamatergic synapses occurs in the early postnatal period and coincides with massive wave of astrocytogenesis. Without astrocytes, synapses do not form in vitro, and similarly astrocytes are necessary for synapse formation in vivo (Pfrieger and Barres 1997; Eroglu and Barres 2010). Astrocytic support on synaptogenesis is mediated by the release of several factors, such as cholesterol, needed for membrane formation (Mauch et al. 2001), thrombospondins (Eroglu et al. 2009) estradiol, protocadherins or integrins (Pfrieger 2010). Astrocytes also produce and release hevin, which promotes the formation of excitatory synapses (Kucukdereli et al. 2011). Synaptic maturation also depends on astrocytic factors such as activity-dependent neurotrophic factor and tumour necrosis factor α, which regulate the trafficking of glutamate receptors to postsynaptic membranes (Eroglu and Barres 2010) and glypicans 4 and 6 that up-regulate the density of AMPA-type glutamate receptors at postsynaptic sites (Allen et al. 2012). Astrocytes

maintain synaptic transmission through numerous homeostatic cascades and membrane transporters that control clearance of neurotransmitters and supply neuronal terminals with neurotransmitter precursors (such as glutamine or L-serine). Finally, astrocytes contribute to synaptic elimination by labelling terminals with complement factor C1q, which is recognised by microglia as an 'eat-me' signal that initiates synaptic pruning (Kettenmann et al. 2013).

Astrocytes Protect Nervous Tissue Against Reactive Oxygen Species

Nervous tissue has exceptional energy demands. The human brain, while representing only 2% of the body mass, consumes >20% of organism energy; most of this energy fuels NKA-dependent redressing of ionic gradients (Magistretti 2009). This high-energy consumption is associated with excessive production of ROS that need to be scavenged and neutralised. The anti-oxidant system of the nervous tissue mostly relies on glutathione and ascorbic acid (Makar et al. 1994). In the brain the bulk of glutathione is concentrated in astrocytes (Dringen et al. 2000), while neuronal synthesis of glutathione relies on astrocytes providing obligatory precursors cysteine or glutamylcysteine. Astrocytes accumulate cystine through the Sxc^- glutamate/cystine exchanger, which is not expressed in neurones. Subsequently cystine is reduced to cysteine, which is further converted to glutamylcysteine (CysGlu) and glutathione. Astrocytes release cysteine which is shuttled to neurones (Chen and Swanson 2003). In the presence of astrocytes, in vitro neurones sustain high levels of glutathione, whereas removal of astrocytes instigates ROS neuronal damage (Dringen et al. 1999). Astrocytes also act as a reservoir for another anti-oxidant, ascorbic acid, which similarly protects neurones against oxidative stress (Wilson et al. 2000).

Neurogliovascular Unit and the Blood-Brain Barrier

The brain is one of the most vascularised organs in the human body. In addition, the brain vasculature possesses the BBB, which controls the nature of molecules entering the nervous tissue. Neuronal activity is functionally linked to the local circulation, and an increase in neuronal firing initiates focal vasodilatation of arterioles and capillaries, a phenomenon known as functional hyperemia (Mosso 1880; Roy and Sherrington 1890). Astrocytes are active contributors to both the barrier function and regulation of the local blood flow.

Protoplasmic astrocytes divide the grey matter into spatially segregated and relatively independent domains, within which astrocytes integrate neurones, synapses, microglial cells and neighbouring capillaries into the neurogliovascular (also known

as neurovascular) unit (Iadecola 2017). The *glia limitans perivascularis* formed by astroglial endfeet cover the parenchymal part of brain vessels almost entirely (Mathiisen et al. 2010). The endfeet are functionally coupled to capillaries through the release of vasoconstrictors and vasodilatators, which include derivatives of arachidonic acid. In addition, the vascular tone can be regulated by local release of K^+ (Zonta et al. 2003; Mulligan and MacVicar 2004; Filosa et al. 2006). Astrocytes can also function as intracranial baroreceptors contributing to the regulation of arterial blood pressure (Marina et al. 2020).

Astrocytes also form the parenchymal part of BBB. The barrier as such is created by the specialised brain capillary endothelial cells which are (together with pericytes and vascular smooth muscle cells) integrated into neurogliovascular unit. The contacts between brain endothelial cells are sealed with tight and adherent junctions, while several transporting systems ensure BBB permeability for selected molecules, which are allowed to enter the brain parenchyma (Sweeney et al. 2019). At the capillary level, astroglial endfeet, endothelial cells and pericytes share a common basement membrane. At the level of arteriolae, two basement membranes, the parenchymal (in contact with astroglial endfeet) and vascular (in contact with endothelial cells), create the perivascular space. Astrocytes are secreting numerous factors that control formation and maintenance of the BBB (Sweeney et al. 2019); in pathology, astroglia support dwindles which impairs the integrity of the barrier (Kriauciunaite et al. 2021).

Astrocytes and Gliotransmission

Astrocyte-neurone signalling, a.k.a. 'gliotransmission' (Santello et al. 2012; Verkhratsky et al. 2016), modulates synaptic transmission/plasticity at tripartite synapses as a part of the synaptic cradle (Perez-Alvarez and Araque 2013). Among the processes regulated by gliotransmission are sleep regulation (Haydon 2017), respiration (Sheikhbahaei et al. 2018) and learning/memory (Gibbs et al. 2011). Gliotransmission is a result of the astrocytic capacity to release several neurotransmitters and neuromodulators, which include ATP, glutamate, GABA, taurine and kynurenic acid. This release occurs through several pathways, which have been characterised in situ and in vitro astroglial preparations and include exocytotic (vesicular) release, diffusion through plasmalemmal channels (e.g. through unpaired connexons, i.e. hemichannels, or several types of large anion/cation channels), via reversed neurotransmitter transporters or previously mentioned cystine-glutamate exchangers (Verkhratsky et al. 2016).

Astrocytes and the Glymphatic System

The brain has a specialised system for the removal of soluble waste products known as a glymphatic system (Iliff et al. 2012; Nedergaard 2013). This system utilises perivascular space between parenchymal and vascular basement membranes and astrocytic AQP4 channels concentrated at the perivascular endfeet to create fluid flow through the brain parenchyma. This fluid flow is instrumental for interstitial solute clearance and is critical for the normal function of the brain. In pathology, under stress or in ageing, the glymphatic subsystem is often impaired; deficient glymphatic clearance contributes to the pathophysiology of several brain disorders including neurodegenerative and psychiatric diseases (Liang et al. 2020; Nedergaard and Goldman 2020).

Envoi

We have tersely summarised the morphology and function of astroglia. We presented them as a group of ectodermal cells with diverse morphology and specific functions, superordinate to the principle function of maintaining homeostasis of the central nervous system. We consider this summary as a necessity in order to better understand a possible role of these cells in pathophysiological condition and diseases.

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Principles of Astrogliopathology

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Pathological Potential of Neuroglia

The pathological potential of neuroglia was widely recognised and acknowledged by neurologists and neuroanatomists at end of the nineteenth and the beginning of the twentieth century. Contribution of neuroglia to the diseases was described, and numerous pathological morphological types of glial cells have been characterised in detail (Achucarro 1910; Alzheimer 1910; Frommann 1878; Nissl 1899). By 1920 the universal involvement of neuroglia in neuropathology was universally accepted; neurologists agreed that "the appearance of neuroglia serves as a delicate indicator of the action of noxious influences upon the central nervous system" (del Río-Hortega and Penfield 1927); the concept of reactive gliosis has been formulated and

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generally recognised (del Río-Hortega and Penfield 1927; Penfield 1928b). The widespread role and importance of neuroglia in neurological and neuropsychiatric diseases were somewhat forgotten in the course of the twentieth century. However, the recently passed decade witnessed much revival in the interest in glia in neuropathology as the neuroglial cells are firmly considered as key players in pathophysiology of all disorders of the nervous system (both central and peripheral), and neuropharmacology regards neuroglia as a legitimate target for new therapeutic strategies (Burda and Sofroniew 2014; Ferrer 2018; Giaume et al. 2007; Parpura et al. 2012; Pekny et al. 2016; Sofroniew 2014b; Verkhratsky et al. 2012b, 2016a, 2017; Verkhratsky and Parpura 2016; Zeidan-Chulia et al. 2014).

Astrogliopathology: General Principles

Astrocytes are primary homeostatic cells of the central nervous system (CNS; see previous chapter); in addition, astrocytes contribute to brain defence. Astrocytic contribution to neuropathology can be primary (when cell-autonomous changes drive the pathologic progression) or secondary, when astrocytes respond to lesions or to various pathological changes in the nervous tissue. Current classification (Fig. 1) distinguishes the following forms of astrogliopathology: (i) reactive astrogliosis, (ii) astrocytic atrophy with loss of function, (iii) pathological remodelling of astrocytes and (iv) astrodegeneration (Fig. 1, (Verkhratsky et al. 2017). These pathological groups cover multiple pathological phenotypes which are yet to be fully characterised; furthermore pathological changes in astrocytes can occur together or in isolation; they are sometimes specific to disease stages and they are affected by age and systemic pathologies.

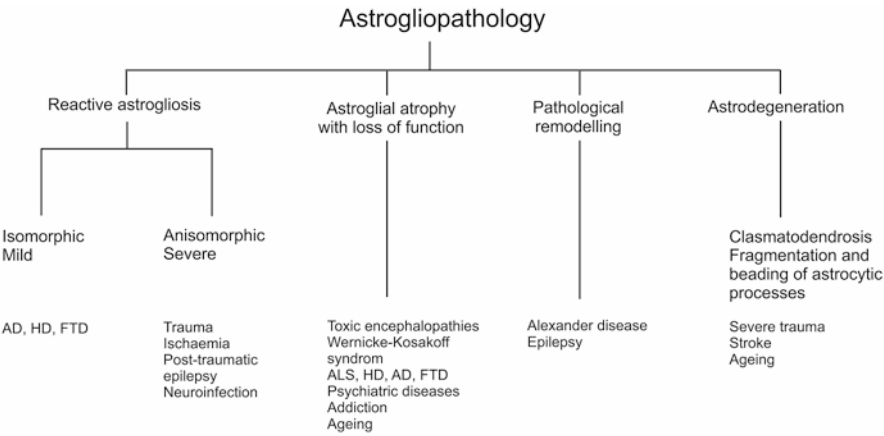

Fig. 1 Classification of astrocytic pathological changes. AD Alzheimer's disease, ALS amyotrophic lateral sclerosis, FTD fronto-temporal dementia, HD Huntington's disease

Reactive Astrogliosis

Reactive astrogliosis is a specific and evolutionary conserved (from arthropods to humans) response of astrocytes to polyaetiological brain lesions, from trauma and infection to neurodegeneration. Reactive astrogliosis is a process whereby, in response to pathology, astrocytes launch genetic programmes that result in biochemical, morphological, metabolic and physiological remodelling (Escartin et al. 2021). This remodelling leads to either gain or loss or modification of astrocytic functions, all aimed at neuroprotection and preservation of the nervous tissue integrity. Astrogliotic remodelling of astrocytes leads to an emergence of multiple context-specific reactive phenotypes, characteristic for particular, age, type of pathology and brain region. These multiple phenotypes differ in specific molecular profile, functions and distinct impact on diseases (Pekny et al. 2016; Sofroniew 2014a; Sofroniew 2020; Verkhratsky et al. 2017). Reactive astrogliosis is flexible to adapt functional and biochemical reprogramming of astrocytes to the nature and strength of the insult with an ultimate goal to mount maximal protection. Within the framework of the same pathology and even within the same affected areas, astrocytes remain heterogeneous in their expression of transcription factors, inflammatory agents and signalling molecules, arguably associated with distinct reactive phenotypes (Garcia et al. 2010; Herrmann et al. 2008).

Reactive astrogliosis contributes to many neurological diseases. In particular, prominent astrogliosis occurs in disorders associated with direct lesion to the nervous tissue by physical, biological or chemical agents. These conditions include neurotrauma (Burda et al. 2016; Faulkner et al. 2004), systemic inflammation and sepsis (Shulyatnikova and Verkhratsky 2019; Tremblay et al. 2020), microbial or viral neuroinfection (Soung and Klein 2018; Zorec et al. 2019), toxic encephalopathies (Li et al. 2021; O'Callaghan et al. 2014), autoimmune inflammation of the nervous tissue including multiple sclerosis (Voskuhl et al. 2009; Wheeler and Quintana 2019), cancerous growth (Henrik Heiland et al. 2019) and neurodegenerative diseases (Verkhratsky et al. 2010). Histopathologically reactive astrogliosis is characterised by morphological hypertrophy, changes in the thickness of processes, sometimes associated with retraction of distal leaflets (Plata et al. 2018); furthermore, reactivity is manifested by an up-regulation of two major cytoskeletal intermediate filaments, glial fibrillary acidic protein (GFAP) and vimentin (Hol and Pekny 2015; Pekny and Pekna 2014; Sofroniew 2014a).

There are several classifications of reactive astrogliosis (Fig. 2). According to morphological changes, astrogliosis is classified into isomorphic and anisomorphic astrogliosis. In isomorphic astrogliosis, astrocytes become hypertrophic; however, they do not move and do not proliferate and the reach of their individual territorial domains remains unchanged (Escartin et al. 2021; Wilhelmsson et al. 2006). Isomorphic astrogliosis is fully reversible, and after the resolution of pathology, astrocytes return to physiological morphology; the isomorphic astrogliosis is indispensable for post-lesion regeneration (Anderson et al. 2016). In anisomorphic astrogliosis astrocytes start to proliferate, and they migrate towards the site of lesion,

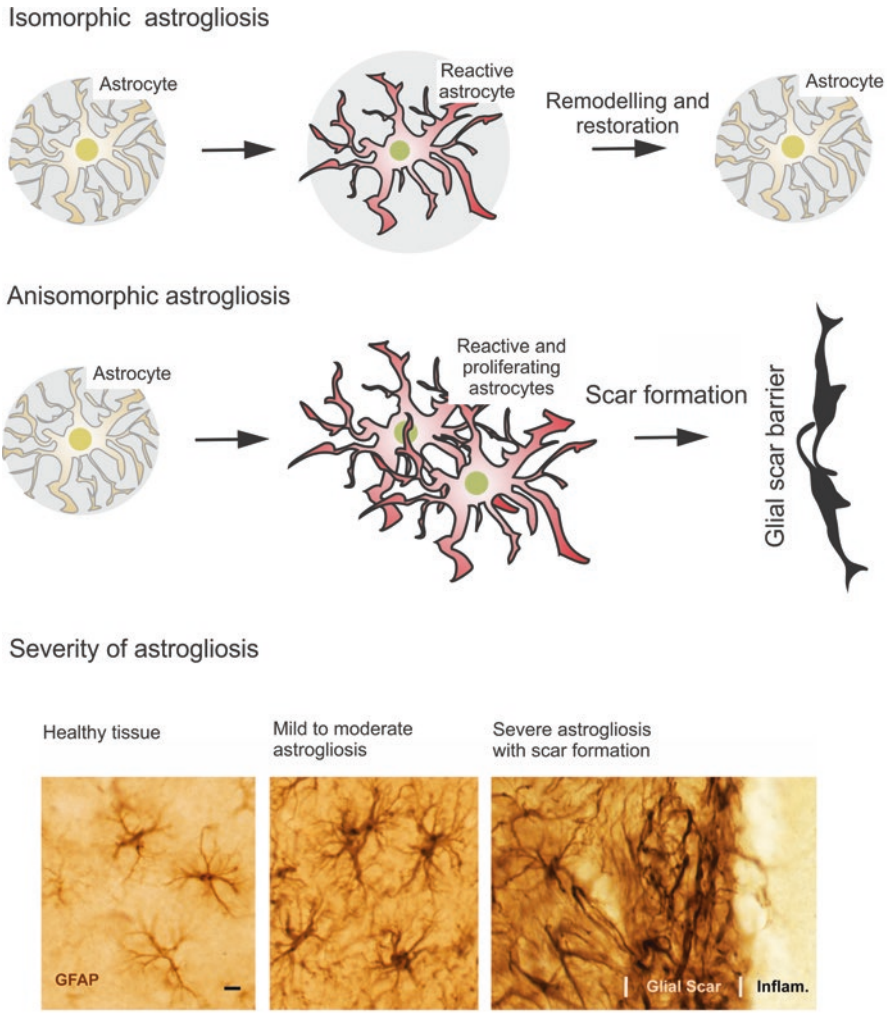

Fig. 2 Classification of reactive astrogliosis; see text for explanation. (Modified from Verkhratsky and Butt (2013) and Sofroniew (2009))

assemble into astroglial palisades and form the glial scar (Pekny et al. 2016; Sofroniew 2020). Another classification divides astrogliosis according to the severity of changes. According to this classification astrogliosis is classified into (i) mild to moderate astrogliosis, (ii) severe diffuse astrogliosis and (iii) severe astrogliosis with compact scar formation (Sofroniew 2009, 2014a). Although morphological presentation of reactive astrocytes can be similar in different pathological contexts generally following the above classification, their molecular signatures are quite distinct and disease-specific. Different astrocytic transcriptomes associate with different conditions and diseases including neurotrauma (Anderson et al. 2016), stroke

(Zamanian et al. 2012), animal models of multiple sclerosis (Itoh et al. 2018) or neurodegenerations; in the latter group astrocytes in Huntington's disease (Al-Dalahmah et al. 2020) are distinct from astrocytes in Alzheimer's disease (Kamphuis et al. 2015). Similarly, astrocytic reactive phenotypes can be different in different stages of the same disease (Wheeler et al. 2020; Zamanian et al. 2012).

Fundamentally, astrogliosis is a defensive response of astrocytes aimed at (i) neuroprotection and trophic support of neural cells tissue, (ii) isolation of the lesioned area, (iii) reconstruction of the compromised blood-brain barrier and (iv) facilitating the post-lesion regeneration of the nervous tissue (Sofroniew 2020). The ultimate result of severe astrogliosis, the scar formation, is essentially defensive reponse to isolate the damaged part of the nervous tissue and save the whole at the expense of its part (Pekny et al. 2016; Verkhratsky et al. 2017; Verkhratsky and Butt 2013). Inhibition of astroglial reactivity often exacerbates the damage to the nervous tissue and worsens neurological outcomes (Pekny et al. 2016). For example, suppression of astrogliotic response increases the size of the traumatic lesions and augments neurological deficit (Okada et al. 2006). Genetic deletion of GFAP and vimentin, both of which are critical for mounting reactive astrocyte remodelling, facilitates the evolution of brain ischaemia (Li et al. 2008) and potentiates posttraumatic synaptic loss (Pekny et al. 1999). Furthermore, inhibition of astroglial reactivity results in higher accumulation of β-amyloid and reduced microglial association with senile plaques in the animal model of Alzheimer's disease (AD); all these changes seem to exacerbate AD-type pathology (Kraft et al. 2013).

Reactive astrogliosis is instigated by multiple factors. Conceptually, astrocytes may sense and integrate numerous molecular cues that signal the damage and provide some information about the nature of this damage. Such molecular cues can have multiple origin and nature. They can be released by damaged cells, they can be associated with accumulation of pathological material (β-amyloid being a well-known example), they can be blood-borne (blood cells or proteins, such as albumin or thrombin) and they can be associated with invading pathogens (bacteria, viruses or prions) or systemic immune factors. Astrogliosis can also be stimulated by certain neurotransmitters and hormones (Fig. 3; (Pekny et al. 2016, Sofroniew 2020)). Conceptually, all factors associated with the instigation of astrogliosis can be classified into (Tang et al. 2012) damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs). The DAMPs are molecules released from immune-responsive microglia or other stressed, damaged or dying cells or factors coming from the circulation through the compromised blood-brain barrier. These factors may include cytokines, chemokines, endothelins, blood-borne proteins, etc. Astrocytes express a wide pattern of receptors that can be activated by DAMPs (Verkhratsky and Nedergaard 2018). The archetypal DAMP is represented by ATP, which is massively released from damaged cells; in pathological contexts, ATP mainly acts on astrocytes through activation of $P2X_7$ purinoceptors, although other classes of purinoceptors may also contribute (Franke et al. 2012). The PAMPs are exogenous agents associated with pathogens such as bacteria, viruses or prions; these factors stimulate Toll-like receptors (TLRs) widely expressed in astrocytes (Jack et al. 2005; Kielian 2006). In addition, astrocytes express nucleotide-binding

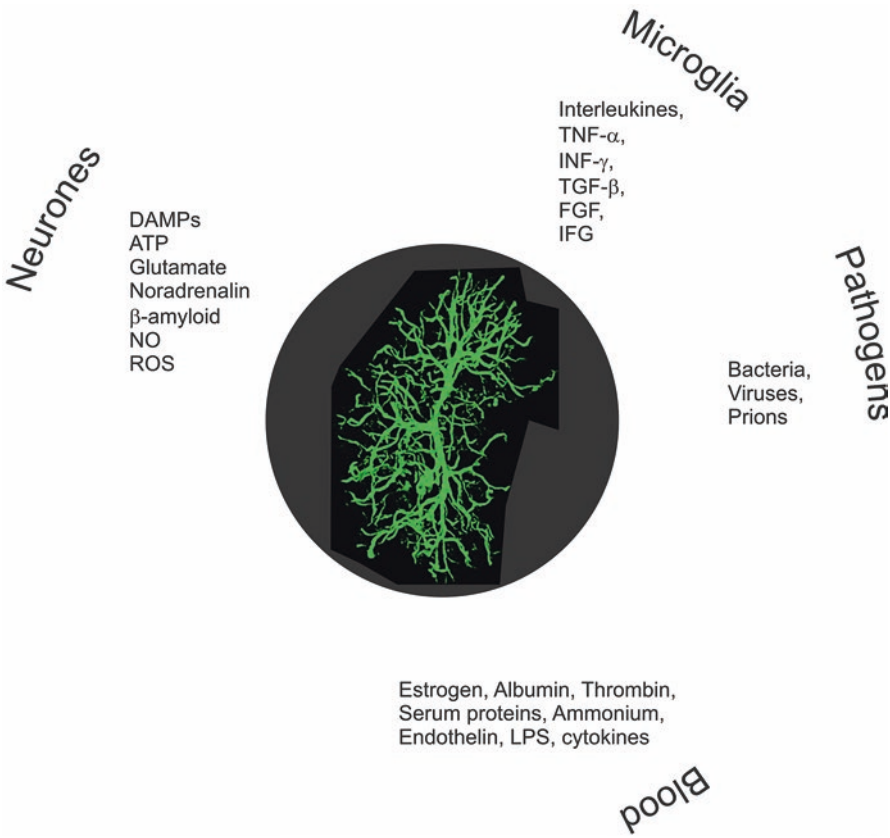

Fig. 3 Instigators of reactive astrogliosis. Numerous agents, including damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPS, pathogens), the former originating from various cells in the nervous tissue or from blood. All these agents can activate various astrocytic receptors which launch astrogliotic programmes. Abbreviations: TNF-α tumour necrosis factor α, INF-γ interferon γ, TGF-β transforming growth factor β, FGF fibroblast growth factor, IFG insulin growth factor, NO nitric oxide, ROS reactive oxygen species, LPS lipopolysaccharide

oligomerisation domain (NOD)-like receptors (NLRs), double-stranded RNA-dependent protein kinase, scavenger receptors, mannose receptor and receptors for complement components and mediators, such as CXCL10, CCL2, interleukin-6 and B-cell-activating factor of the TNF family, all of which are contributing to the regulation of reactive astrogliosis (Farina et al. 2007).

Intracellularly, initiation of reactive astrogliosis is associated with Ca^{2+} signalling. This signalling is an important part of astrocytic intracellular excitability, mediated by cytosolic ions and second messengers (Verkhratsky et al. 2020b, c). Exposure of astrocytes to various DAMPs and PAMPs is frequently associated with initiation of Ca^{2+} signals mainly originating from Ca^{2+} release from the intracellular

endoplasmic reticulum (ER) Ca^{2+} store. This release is mediated by inositol-1,4,5,-trisphosphate ($InsP_3$) receptor type 2, which is predominant in astrocytes (Verkhratsky et al. 2012a). Similarly, pharmacological inhibition of Ca^{2+} release from the ER suppressed astrocytic reactivity in response to β-amyloid (Alberdi et al. 2013)

Despite being an intrinsically defensive response, reactive astrocytes may, in certain conditions, acquire maladaptive features which may exacerbate or even cause damage to the nervous tissue (Pekny et al. 2016; Sofroniew 2020). First, astrocytic reactivity may interfere and downregulate essential homeostatic functions such as K^+ buffering or glutamate homeostasis. In particular, failure of glutamate homeostasis seems to be a converging point in the pathophysiology of various neurological diseases, such as toxic encephalopathies (Li et al. 2021), hepatic encephalopathy (Montana et al. 2014; Obara-Michlewska et al. 2015), epilepsy (Bedner et al. 2015) or amyotrophic lateral sclerosis (Rossi et al. 2008; Valori et al. 2014). In addition, reactive astrocytes may be associated with the release of potentially damaging molecules through pathological gain of function, when existing homeostatic cascades start to overproduce particular agents. For example, in Alzheimer's disease astrocytes overexpress monoamine oxidase-B (MAO-B) to produce GABA from putrescin; this overproduction of GABA counteracts neuronal hyperexcitability closely associated with AD progression (Garaschuk and Verkhratsky 2019; Ghatak et al. 2019). Increase in MAO-B activity, however, results in overproduction of hydrogen peroxide that initiates neuronal damage and death (Chun et al. 2020). Similarly, astrocytic overproduction of complement C3 (which otherwise is a legitimate physiological ligand) leads to morphological and functional neuronal defects (Lian et al. 2015).

To summarise, reactive astrogliosis is an intrinsic physiological astrocyte programme aimed at neuroprotection, at maintenance of tissue homeostasis and at preservation of integrity of nervous tissue. In certain conditions, however, and in particular in conditions of chronic and severe stress, reactive astrocytes may acquire maladaptive properties contributing to the damage of the CNS. In both conditions, reactive astrocytes remain an important part of disease progression often defining the neurological outcome of neuropathological process.

Pathological Remodelling of Astrocytes

The second group of astrogliopathologies is represented by pathological remodelling of astrocytes. This class of pathological changes covers astrocytic abnormalities associated with an acquisition of aberrant molecular cascades or functional properties, which drive pathology (Ferrer 2018; Pekny et al. 2016). The best examples of pathological astrocytic remodelling are represented by primary genetic astrogliopathies linked to expression of mutated genes. Alexander disease, a genetic leukomalacia, stems from astrocytic expression of sporadically mutated GFAP

gene, which affects, in a yet unknown way, astrocyte function which ultimately results in severe damage to the white matter (Messing et al. 2012). Another example of pathological remodelling of astrocytes occurs in Duchenne muscular dystrophy (DMD) associated with expression of mutated dystrophin gene. Although major clinical presentation of DMD is associated with muscular weakness and cardiomyopathy, most of the patients show psychosocial abnormalities and impaired cognitive abilities. In the CNS dystrophin is expressed mainly in astrocytes (Hendriksen et al. 2016), and its mutations are linked to aberrant CNS cyto-architecture, abnormalities in dendrites and loss of neurones. All these cytopathologies cause a general detrimental neurobehavioural profile, including attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders and obsessive-compulsive disorder (Anderson et al. 2012; Hendriksen et al. 2018; Ricotti et al. 2015). At the cellular level, expression of mutant dystrophin gene resulted in an aberrant cytoskeleton arrangement and deficient homeostatic capabilities of astrocytes derived from stem cells isolated from DMD patients. In particular, glutamate clearance was severely affected in these astrocytes (Patel et al. 2019). Astroglial pathological remodelling is also central for several other leukodystrophies including vanishing white matter disease, megalencephalic leukoencephalopathy with subcortical cysts and Aicardi-Goutières syndrome (Brignone et al. 2014; Dooves et al. 2016; Jorge and Bugiani 2019). Finally, pathological remodelling of astrocytes has been suggested to occur in mesial temporal lobe epilepsy, characterised by aberrant astrocytic morphology, reduced gap junctional coupling and downregulation of $K_{ir}4.1$ channel expression; all these changes converge into deficient K^+ homeostasis that facilitates generation of seizures (Bedner et al. 2015).

Astroglial Atrophy, Asthenia and Loss of Function

This class of pathological changes includes cell-autonomous astrocytic changes, which do not involve reactivity (i.e. they are not instigated by lesion to the CNS) while being associated with diminished astrocytic function. First, this astrocytic insufficiency is linked to cellular atrophy manifested by decrease in astrocytic morphological profile, with corresponding decrease in astrocytic territorial domain and diminished astrocytic synaptic coverage. This morphological atrophy associated with decrease astrocytic homeostatic support is observed in numerous neuropathological contexts. In particular, morphological atrophy of astrocytes has been detected in diseases of cognition such as neurodegenerative diseases (Heneka et al. 2010; Rodriguez et al. 2009; Verkhratsky et al. 2010) and psychiatric diseases (Dietz et al. 2020; Verkhratsky et al. 2014; Verkhratsky and Parpura 2016; Windrem et al. 2017). Major neuropsychiatric disorders, such as schizophrenia, major depressive disorder and addictive disorders are all associated with reduction of astrocytic density and decrease in astrocytic morphological profiles as revealed by multiple markers (Cotter et al. 2001; Czeh and Di Benedetto 2013; Czeh and Nagy

2018; Miguel-Hidalgo 2009; Rajkowska et al. 2002; Rajkowska and Stockmeier 2013; Scofield et al. 2016). Another pathological feature, the astrocytic asthenia, which is manifested by failures of astroglial homeostatic cascades, is also frequently present in diseases of the brain. In particular, severe decrease in glutamate clearance due to ~80% decrease in expression of astrocytic plasmalemmal glutamate transporters is a leading cause of Wernicke-Korsakoff encephalopathy, associated with massive excitotoxic neuronal death (Hazell 2009; Hazell et al. 2009). Deficits in astroglial glutamate clearance and failure in glutamate-glutamine/GABA shuttle are likely responsible for abnormal neurotransmission as well as for excitotoxic neuronal death, both resulting in psychotic symptoms (Sanacora and Banasr 2013). Decreased expression of plasmalemmal glutamate transporters and decreased glutamate clearance from the extracellular space/synaptic cleft are common features of many addictive disorders, with astrocytic plasmalemmal glutamate transporters representing a promising drug target (Roberts-Wolfe and Kalivas 2015). Neuronal death in amyotrophic lateral sclerosis similarly reflects astrocytic loss of function being a consequence of insufficient astroglial function in extracellular glutamate clearance (Rossi et al. 2008; Valori et al. 2014).

Atrophy of astrocytes linked to decreased synaptic connectivity and synaptic efficacy contributes to cognitive deficiency in both normal ageing and senile dementia. Ageing is the main risk factor for neurodegenerative diseases underlying senile dementia, including Alzheimer's disease. At the same time normal physiological brain ageing with mostly preserved cognitive capacity differs fundamentally from neurodegenerative pathology: in the former the number of neurones is largely preserved, whereas in the latter neurones undergo massive death, which underlies severe cognitive impairment (Pakkenberg and Gundersen 1997; Verkhratsky et al. 2004; von Bartheld et al. 2016; West 1993). Astrocytic numbers seem to be preserved in physiological ageing, whereas the data on astrocytic morphology are controversial and detailed analysis of astrocytic profiles is scarce (Olabarria et al. 2010; Pakkenberg and Gundersen 1997; Verkhratsky et al. 2020a). Most of our knowledge of the state of astrocytes in the ageing brain rests on the analysis of the expression of GFAP, the presumed universal marker of astrocytes (Hol and Pekny 2015). Expression of GFAP is generally increased in the aged brain, which was considered as a sign of astrogliosis and age-dependent inflammation (David et al. 1997; Goss et al. 1991; Hardy et al. 2018; Nichols et al. 1993). Morphometry of aged astrocytes, however, revealed rather contradictory results with both increase and decrease in size and complexity of GFAP-positive astrocytic profiles being observed (see Verkhratsky et al. (2020a) for details and references). All these results, however, need a critical revisit, because GFAP is not an ideal marker of astrocytes (see Verkhratsky and Nedergaard (2018) for detailed discussion). First, in a healthy brain, the majority of astrocytes do not express GFAP at the level of immunocytochemical detection. Second, the proportion of GFAP-positive cells depends on age and brain region. Third, increases in GFAP immunoreactivity does not necessarily report reactive changes; in the suprachiasmatic nucleus and the intergeniculate leaflet, for example, GFAP expression undergoes substantial circadian changes (Moriya et al. 2000). Fourth, GFAP labels only

cytoskeleton associated with primary astrocytic processes; the peripheral leaflets are always GFAP-negative, and therefore GFAP cannot accurately reveal astrocytic morphology. Finally, GFAP expression changes under various types of environmental stimulation: physical exercise or environmental enrichment increases GFAP-positive profiles, and this increase is beneficial for nervous tissue (Diniz et al. 2016; Rodriguez et al. 2013; Sampedro-Piquero et al. 2014). Thus, age-dependent changes in GFAP expression and GFAP-positive profiles do not reveal much about astrocytic ageing.

Labelling of astrocytes with other markers showed more complex age-dependent changes. Staining of astrocytes with Golgi black reaction did not identify age-dependent morphological changes (Castiglioni Jr. et al. 1991). Immunohistochemical analysis of astroglial profiles labelled with antibodies against GFAP, glutamine synthetase and protein s100β demonstrated complex region- and marker-dependent and age-dependent changes ranging from atrophy to hypertrophy (Rodriguez et al. 2014). The GFAP-labelled astrocytes showed hypertrophy in the CA1 region and in the dentate gyrus of old hippocampus but marked atrophy in the entorhinal cortex (EC). Astrocytes positive for glutamine synthetase were smaller in old hippocampus but larger in the old entorhinal cortex, while s100β-positive profiles from old animals demonstrated an increase in the entorhinal cortex and almost no change in the dentate gyrus and no changes in the CA1 region (Fig. 4).

Morphology of astrocytes probed with intracellular injection of the fluorescent dye Alexa Fluor® 594 revealed age-dependent changes in astrocytic morphology. Two-photon imaging with subsequent 3D reconstruction of astrocytes perfused with

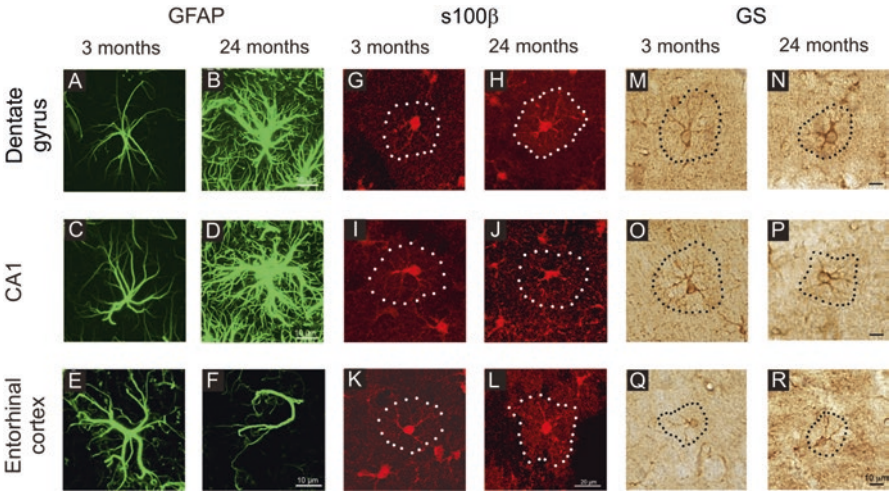

Fig. 4 Age-dependent remodelling of astroglial profiles in different brain areas. Confocal images showing glial fibrillary acidic protein (GFAP) (A to F), s100β (G to L) and glutamine synthetase (GS) (M to R) immunolabelled astrocytes in the dentate gyrus and CA1 hippocampal areas as well as in the entorhinal cortex of mice at 3 and 24 months. (Reproduced, with permission from Verkhratsky et al. (2020a))

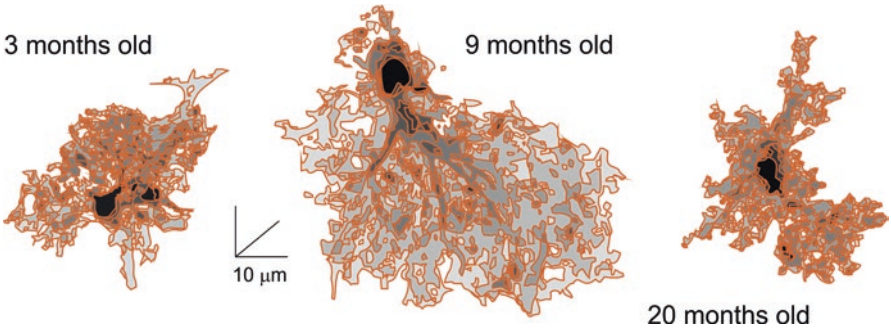

Fig. 5 Reconstructions of hippocampal protoplasmic astrocytes from young, adult and old mice. (Reproduced, with permission from Verkhratsky et al. (2020a))

the dye showed a significant increase in the size and complexity of astrocytes in development from youth to adulthood, whereas astrocytes in the old brains were smaller and less complex and significant decrease in size and complexity of astrocytes in old animals, with substantial reduction on the volume of peripheral processes (Fig. 5, (Popov et al. 2020)). These changes in peripheral processes affected synaptic coverage and synaptic homeostasis; in particular, astrocytic extracellular glutamate and K^+ clearance are both compromised in old animals, leading to depression of long-term potentiation reflecting on deficient memory (Popov et al. 2020).

Astrocytic atrophy is also present in neurodegenerative diseases. In AD, atrophic astrocytes appear in the brain together with reactive astrocytes. Subpopulations of atrophic astrocytes have been found in transgenic AD mouse models (Beauquis et al. 2013; Olabarria et al. 2010) and confirmed in stem cell-derived astrocytes from AD patients in vitro (Jones et al. 2017; Mohamet et al. 2018) and in vivo in derived astrocytes grafted in the mouse brain (Preman et al. 2020). In AD mouse models the total number of astrocytes does not change with age (Olabarria et al. 2010, 2011). At the same time at the early, pre-plaque, stages, astrocytes in entorhinal and prefrontal cortices and hippocampus demonstrate morphological atrophy (Beauquis et al. 2013; Kulijewicz-Nawrot et al. 2012; Olabarria et al. 2010; Yeh et al. 2012). There is a specific temporal pattern in the emergence of atrophic astrocytes in mouse AD models (Rodriguez et al. 2016; Verkhratsky et al. 2019). First, atrophic astrocytic profiles (as visualised by antibodies against GFAP, s100β or glutamine synthetase) appear in the entorhinal cortex (they are present already in 1-month-old mice); subsequently, atrophic astrocytes appear in the prefrontal cortex (3–4 months of age) and finally in the hippocampus (in 6- to 9-month-old animals). Appearance of atrophic astrocytes thus precedes formation of β-amyloid deposits.

At the later stages (12- to 18-month-old animals) of AD, the emergence of β-amyloid plaques in the hippocampus instigates astrogliotic remodelling; reactive astrocytes migrate towards and surround senile plaques and β-amyloid infested blood vessels; at the same time atrophic astrocytes are positioned distantly to β-amyloid depositions (Olabarria et al. 2010; Verkhratsky et al. 2016b). Conversely,

in entorhinal and prefrontal cortices, extracellular β-amyloid depositions are not accompanied with astroglial reactivity (Verkhratsky et al. 2016b). Failed astrogliosis represents a loss of function, which defines vulnerability of different brain regions to AD pathology. Indeed, in humans AD starts in entorhinal and prefrontal cortices before this disease spreads to the hippocampus.

Astrocytic atrophy and loss of function can contribute to AD pathophysiology being responsible for early synaptic dysfunction and cognitive deficits. Atrophic astrocytes provide diminished synaptic coverage, which translates in decreased support of synapses by astroglial cradle. First and foremost, this affects K^+ buffering and glutamate homeostasis which both are critical for normal synaptic connectivity. In addition, astrocytes are fundamental for synaptogenesis not only in the developing but also in the adult brain, and astrocytic atrophy may impair the formation of new synapses associated with learning and neuronal plasticity. Early stages of AD are associated with synaptopathy (Coleman et al. 2004; Terry 2000), which might be directly linked to diminished astrocytic support. Astroglial asthenia and loss of function may also account for deficient support associated with the lactate shuttle. Finally, a failure of astrogliotic defence together with a loss of homeostatic capacity of astrocytes (the glial paralysis) can be directly linked to neuronal death and brain atrophy clinically manifested as senile dementia (Verkhratsky et al. 2015).

Astrodegeneration or Clasmatodendrosis

Insults to the brain as well as chronic brain pathologies stress astrocytes, which can undergo degenerative changes and necrotic or apoptotic death. Morphologically, astrodegeneration is manifested by clasmatodendrosis (from Greek “κλάσμα”, fragment, “δένδρον”, tree, “ωσις”, process). This process has been initially characterised by Alois Alzheimer and also described and named by Santiago Ramón y Cajal (Penfield 1928a). Clasmatodendrosis appears as fragmentation of astroglial processes, vanishing of distal processes, and swelling and vacuolisation of the cell body. Clasmatodendrosis has been visualised in vitro and in tissue, and it was observed in several forms of neuropathology including ischaemia, infectious encephalopathies, stroke, dementia and psychiatric diseases (Hulse et al. 2001; Sahlas et al. 2002; Tachibana et al. 2019). Clasmatodendrotic astrocytes have been also identified in the brains of old mice (Mercatelli et al. 2016).

Envoi

We have outlined the presently ascribed roles of astroglia in nervous system pathology. As per human need to organize and stratify, we pigeonholed the roles into the present-day classification of astrogliopathology. While we have no doubt that this classification will develop further, likely by the time one reads these lines as the

volume gets published, we deem it necessary and sufficient for further discussion of more detailed chapters that follow in this volume and delve into the role of astroglia in a variety of psychiatric conditions and diseases.

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Morphological Features of Astrocytes in Health and Neuropsychiatric Disorders

Celia Roman, Eugenia Vivi, and Barbara Di Benedetto

Introduction

In the 1850s, Rudolf Virchow first coined the concept of "neuroglia" (or more simply "glia," from the Greek γλία and γλοία which means "glue"), referring to the passive connective fibers and intercellular masses, which embed neurons and appear like glue (Virchow 1858).

In the late nineteenth century, additional observations by the Italian physician and cytologist Camillo Golgi and the Spanish neurohistologist Ramon y Cajal revealed that neuroglia and nerve cells represent distinct cellular populations. Following this theory, they further described a variety of glial shapes and forms, suggesting the existence of different subtypes of glia cells, which may provide a corresponding diversity of functions within the CNS (Golgi 1871).

Yet the term "astrocyte" (from the Greek ἄστρον, ástron, "star" + κύτος, kútos, "cavity," "cell") was only first introduced in 1893 by the Hungarian anatomist and histologist Lenhossek, clearly referring to the stellate morphology of these cells (Lenhossek 1893).

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With this new name, he advanced the concept that astrocytes cover a range of functions as important as nerve cells, thus getting away from the term “brain glue.”

Although astrocytes are in close contact with neuronal structures, it was not clear whether they would be as diverse as neurons. Indeed, already the early histological studies from Ramon y Cajal’s work revealed a high morphologic diversity of astrocytes, suggesting several functional specializations (De Filipe 2010). However, only in the past decade, accumulating evidences indeed showed that astrocytes display a high regional heterogeneity in the developed CNS. This heterogeneity is essential for maintaining, among others, a proper brain architecture, functional homeostasis, and an appropriate delivery of nutritional elements, due to the intimate interaction of astrocytes with a variety of distinct cell types in multiple brain areas and during different developmental or adult stages (John Lin et al. 2017; Kettenmann and Verkhratsky 2008; Liddelow et al. 2017).

Moreover, other studies have demonstrated inter-species morphological and functional distinctions in astrocytes, highlighting the potential contribution of astrocytes to species-specific neuronal processing (Oberheim et al. 2006; Oberheim et al. 2009).

Indeed, it is today recognized that astrocytes display a body of morphological and functional aspects that reflect the brain network in which they are embedded.

Astrocyte Morphological Heterogeneity

Astrocytes account for approximately 20–40% of the total number of brain cells, representing the most abundant glial cells populating the CNS (Herculano-Houzel 2014).

The most remarkable characteristic of astrocyte morphology, which makes them heterogeneous, derives from their process ramification complexity and irregularity. Additionally, astrocyte heterogeneity can be classified on the basis of development, reactive state, regional identity, and age-related diversities.

Since the late nineteenth century, astrocytes were already recognized as a morphologically complex population tiling the CNS. Accordingly, they were already divided into two major classes, still currently in use: protoplasmic astrocytes of the gray matter and fibrous astrocytes of the white matter (Ramón y Cajal 1897) (Kohler et al. 2019) (Fig. 1a, b).

Protoplasmic astrocytes are the more numerous type of astrocytes and are characterized by few thick processes, which branch out into several fine and short processes, widely and uniformly distributed in the gray matter. As a matter of fact, protoplasmic astrocytes can be composed of six to seven main branches originating from the soma, with various secondary branches that can spread into thousands of smaller processes, which establish interactions with other cell types. These fine small processes, termed peripheral processes or perisynaptic astrocyte processes (PAPs), are specialized and polarized structures. In accordance, a protoplasmic astrocyte can be characterized by a diameter of 40–60μm, with approximately 95%

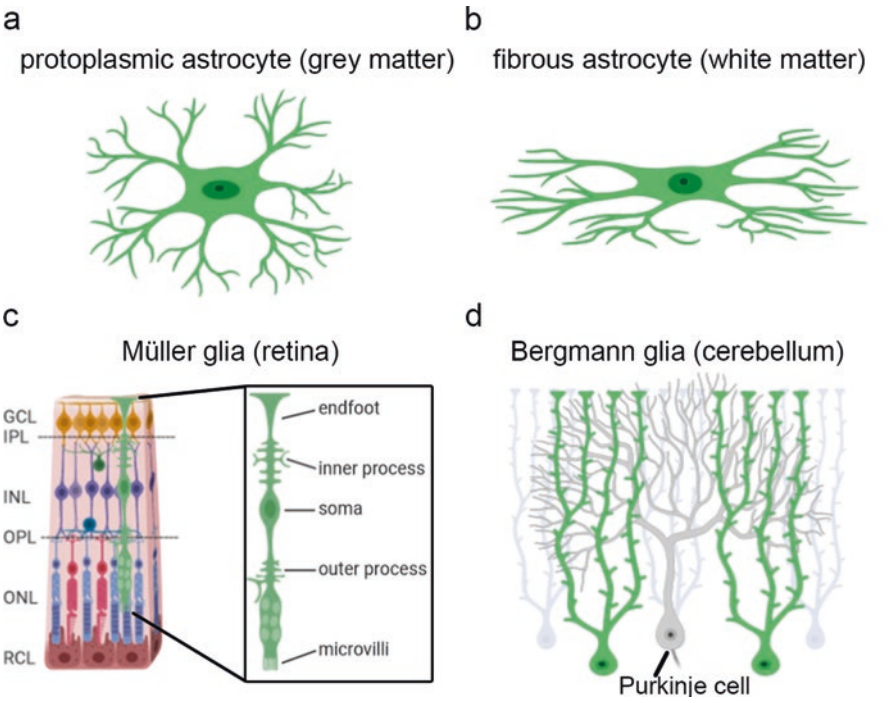

Fig. 1 Astroglia heterogeneity. Astroglia can be grouped in morphologically different subtypes: (**a**) protoplasmic astrocytes of the gray matter; (**b**) fibrous astrocytes of the white matter; (**c**) Müller glia, specific of the retina; and (**d**) Bergmann glia, typical of the cerebellum. GCL ganglion cell layer, IPL inner plexiform layer, INL inner nuclear layer, OPL outer plexiform layer, ONL outer nuclear layer, RCL retinal cell layer (pigment epithelium). (Created with BioRender.com)

of its surface composed of processes. Such a highly ramified body allows them to reach numerous synapses, especially in the hippocampus and cerebral cortex, where they are present in high numbers (Reichenbach et al. 2010).

Interestingly, compared to rodent astrocytes, human protoplasmic astrocytes are up to threefold larger in diameter and extend ten times more primary processes coming into contact with 100-fold more synapses than their rodent counterparts (Bushong et al. 2002; Oberheim et al. 2006).

Although human protoplasmic astrocytes are significantly larger and more complex than the rodent counterpart, they are still similarly organized in non-overlapping domains (Sofroniew and Vinters 2010).

The many fine processes of protoplasmic astrocytes also extend to the microvasculature, enwrapping the wall of blood vessels to form the blood-brain barrier (BBB) (Sofroniew and Vinters 2010). In this way, they develop what is called the "neurovascular unit" (NVU), a functionally complex structure juxtaposed between endothelial cells and neurons (Fig. 2). Moreover, the processes of two adjacent protoplasmic astrocytes occupy non-overlapping domains, with the domain of any

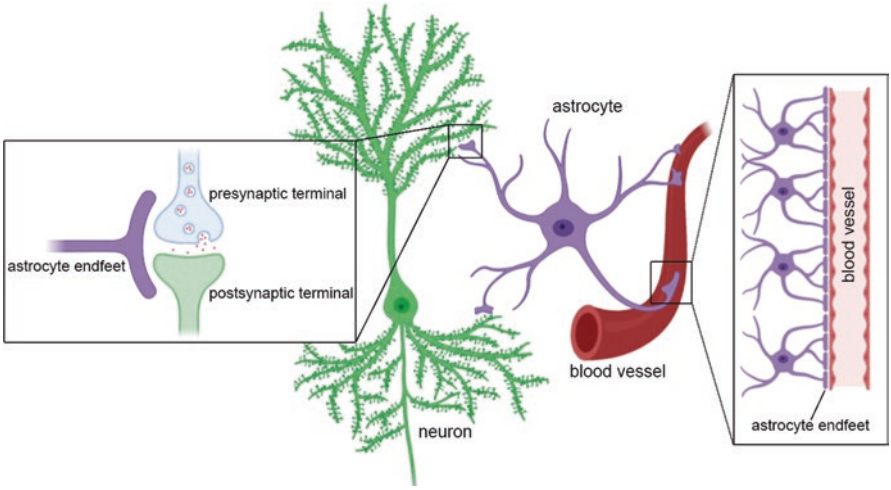

Fig. 2 The neurovascular unit. Astrocyte terminal processes (endfeet) interact on the one side with brain blood vessels to form the blood-brain barrier and on the other side enwrap synaptic terminals to modulate neurotransmission. (Created with BioRender.com)

single astrocyte coordinating specific clusters of synapses (Bushong et al. 2002; Halassa et al. 2007).

In contrast to the protoplasmic, the fibrous astrocytes populate the white matter, the optic nerve, and the retinal nerve fiber layer of mammals. They are morphologically characterized by elongated cell bodies with distinguishable processes, which give rise to long, thin, and less branched secondary/tertiary processes. In addition, they are longitudinally oriented along the plane of the fiber bundles (Miller and Raff 1984). The processes of fibrous astrocytes are typically longer then those of protoplasmic astrocytes. Additionally, the processes of protoplasmic astrocytes envelop synapses and blood vessels, whereas the processes of fibrous astrocytes are in contact with the nodes of Ranvier (Peters et al. 1991). This differentiation becomes relevant when thinking about the distinct functions that various cell types play in either the gray or the white matter. On the one hand, the gray matter's major task is to compute information at neuronal synapses, and for this reason protoplasmic astrocytes' fine processes interact with up to 200,000 synapses in mice and 2 million in humans to modulate synaptic neurotransmission (Oberheim et al. 2006; Sofroniew and Vinters 2010) (Fig. 2). On the other hand, information in the white matter is mainly transmitted along the myelinated axons, with the support of their functionally specialized units, the nodes of Ranvier; thus, fibrous astrocyte processes line up with the axons and connect to these units to modulate long-range axonal neurotransmission. Above all, many of these morphological differences are then further determined by the properties and functions of a given brain region.

In addition to these basic cell types, some specialized astrocytes in different areas of the brain, such as Müller cells and Bergmann glial cells, have been described (Fig. 1c, d).

Müller cells are the principal radial glia of the vertebrate retina (Bringmann et al. 2006). They are the only cells representing the macroglia family in the retina. The processes of Müller cells contact the extracellular clefts and virtually every neuronal and non-neuronal element, such as blood vessels. These specialized radial glial cells form an architectural supporting structure, which extends across the entire thickness of the neural retina, from the vitread surface to the subretinal space. Müller cell bodies are localized in the central nuclear layers of the retina. Their thick and thin processes project to both outer and inner limiting membrane. Interestingly, in the plexiform layers, Müller cell processes appear like those of protoplasmic astrocytes (Bringmann et al. 2006; Reichenbach and Bringmann 2013). Each of these cells ensheathes and supports a columnar "micro-unit" of retinal neurons. The size and shape of Müller cells can vary according to animal species and retinal topography.

Bergmann glia are radially oriented, unipolar astrocytes spanning through the entire thickness of the molecular layer of the cerebellum in all vertebrates (Reichenbach et al. 2010).Their cell bodies reside in between the Purkinje cell somata and extend their processes transversely across the molecular layer to terminate in the pia mater with their endfeet, without reaching the ventricular surface (Yamada and Watanabe 2002). In the pia mater, Bergmann processes are aligned parallel to the long axis of the folium. The processes of Bergmann glial cells display elaborated morphological and functional interactions with the dendritic synapses of the Purkinje cells. Indeed, longitudinal columns of Bergmann glial cells cover the dendritic arbors of each Purkinje cell. The soma of these glial cells are localized between those of Purkinje neurons and their process endfeet in the pia matter. The length of these processes is determined by the thickness of the molecular layer. Interestingly, the thickness of this layer diversifies greatly between different species. In small species the Bergmann glial cell processes are short, whereas in large species they are much longer but less dense (Grosche et al. 2002). It is estimated that on average there are about 8.1 Bergmann glial cells to every Purkinje neuron in the rodent cerebellum. Because of this intrinsic relationship, Bergmann glial cells are involved in the regulation and support of the Purkinje structure and function in the adult cerebellum (Palay and Chan-Palay 1974; Reichenbach et al. 1995).

Furthermore, there are more subtypes of cortical astrocytes exclusively found in human and nonhuman primates, such as the interlaminar astrocytes (ILAs) residing in the layer I and projecting long processes toward multiple laminae, terminating in layer II/IV, and varicose projection astrocytes that reside in layers V–VI (Colombo et al. 1997; Falcone et al. 2019; Oberheim et al. 2009). Interlaminar astrocytes are particularly packed in layer I and display oblong cell bodies with their processes organized in a columnar manner through the cortical layers.

Even though they are primate-specific cells, interlaminar human astrocytes are not only larger in number, but they also exhibit mild morphological differences with

respect to their chimpanzee counterparts (Colombo et al. 1997; Oberheim et al. 2009).

Accordingly, human interlaminar astrocytes are characterized by spheroid cell bodies and several short processes that contribute to the pial glial limitans, creating a thick network of fibers. They extend one or two processes from layer I, resulting in numerous and tortuous millimeter-long processes. Electron microscopy analysis revealed that these endings possess a multilamellar structure and are enriched in mitochondria, suggesting a high metabolic activity (Colombo et al. 1997). The exact function of these cells remains obscure, but their morphological characteristics suggest that they might provide a network for long-distance calcium propagation (Oberheim et al. 2009).

Varicose projection astrocytes, observed in humans and chimpanzee only, are characterized by main processes shorter and straighter than those exhibited by typical protoplasmic astrocytes. Additionally, they frequently extend one to five long, less branched processes of up to 1 millimeter in length, which terminate in the neuropil or on blood vessels. Human varicose projection astrocytes are more complicated and larger than those described in chimpanzee. The processes of varicose projection astrocytes travel in all directions, frequently penetrating the domains of neighboring astrocytes (Colombo et al. 1995; Oberheim et al. 2009). Since varicose projection astrocytes are found only in human and higher-order primates, it is speculated that they might be involved in specific cognitive functions, even though their precise role is still unknown.

In conclusion, astrocytes exhibit a high regional and microenvironmental diversity. However, unlike neurons, it is still a lot more challenging to isolate diverse regional and/or astrocyte subclasses, as astrocytes homogeneously occupy the CNS microenvironment.

Astrocyte Molecular Heterogeneity

Different regions of the adult brain contain highly morphologically heterogeneous classes of astrocytes that define the CNS neuroanatomy (Emsley and Macklis 2006).

Their morphological characteristics and relationship with both neurons and blood vessels vastly influence brain functions in important, region-specific ways. Thus, astrocyte populations highly likely display additional unique molecular signatures, which may correlate with their morphological features. However, while studies on neurons and oligodendrocytes have been smoothed by the existence of subtype-specific markers, astrocyte corresponding molecular signature has not yet been defined. Nevertheless, the glial fibrillary acidic protein (GFAP), a member of the cytoskeletal protein family and thought to be important for modulation of astrocyte morphology and motility, is classically used to discriminate and detect astrocytes within the CNS (Eng 1985).

Even though GFAP has been widely used as a standard marker for astrocytes, several studies have reported the existence of astrocytes with undetectable levels of

GFAP. Additionally, not all cells in the CNS that express GFAP are astrocytes (Kimelberg 2004; Mishima and Hirase 2010). As an example, layer III and IV astrocytes are devoid of GFAP, although astrocytes appear homogeneously distributed in these regions (Gabbott and Stewart 1987). In accordance, fibrous astrocytes of the white matter express high levels of GFAP, whereas protoplasmic astrocytes of gray matter normally express little or no GFAP, except for few locations, such as the CA1 region of the hippocampus. While a number of proteins have been reported to be selectively expressed by astrocytes, not all of them entirely label all and only astrocytes, but are restricted to either their subcompartments or subgroups or are present in other cell types, too. For example, aquaporin 4 (AQP4), a water channel protein involved in maintaining water and ion homeostasis associated with neuronal activity and highly specific for astrocytes, is localized primarily to astrocytes endfeet; connexin 43 (Cx43), a transmembrane protein that forms gap junction channels and hemichannels, only labels some astrocytes and is also expressed in endothelial cells; finally, S100 calcium-binding protein ß (S100ß) involved in cell cycle regulation and cytoskeleton modification, classically thought to be principally expressed by astrocytes, is not found in all astrocytes. Indeed, S100ß is only expressed by a subgroup of mature astrocytes that ensheath blood vessels and by immature and mature oligodendrocytes (Hachem et al. 2005).

Other astrocyte markers commonly used to label astrocytes are: glutamate transporter GLT-1 (or human EAAT2), expressed in developing astrocyte precursors (Rothstein et al. 1994; Shibata et al. 1997); the glutamine synthase (GS), an enzyme that catalyzes the conversion of ammonia and glutamine to glutamate, which is considered highly specific, although it is also found in oligodendrocytes of the white and gray matter (D'Amelio et al. 1990); and the inwardly rectifying K^+ channels like Kir4.1, predominantly confined to the membrane of astrocyte processes surrounding synapses and blood vessels, thus suggesting that Kir channels can carry both K^+-uptake current in astrocytes at synaptic sites and K^+-extrusion current to the blood vessels (Higashi et al. 2001).

Moreover, the major understandings of astrocyte heterogeneity come from transcriptome wide sequencing experiments to reveal the cell molecular machinery. For instance, a seminal study from Doyle and colleagues examined the transcriptome heterogeneity of isolated astrocytes from different brain regions via TRAP (Translating Ribosome Affinity Purification) technique and showed that astrocytes form the cortex and the cerebellum display considerable different gene clustering sets (Doyle et al. 2008).

Similarly, in another study, Morel et al. profiled astroglial ribosome-associated mRNA in the cortex, hippocampus, nucleus accumbens, caudate putamen, thalamus, and hypothalamus. They showed that gene astroglial expression pattern was highly overlapping between cortex and hippocampus, while the nucleus accumbens, caudate putamen, thalamus, and hypothalamus exhibited a unique mRNA expression set not identified in astrocytes from other brain regions (Morel et al. 2017). As an example, Hevin, a pro-synaptogenic protein, and its mRNA were expressed at comparable levels across all regions. However, Sparc, which antagonizes the synaptogenic functions of Hevin, was enriched in thalamic and hypothalamic

astrocytes. This might suggest that cortical or subcortical astrocytes differently promote synaptic development, following a gradient of astrocyte gene expression along the dorsoventral axis.

In addition, isolation of astrocytes from the cortical layers via intersectional labeling approaches has disclosed differences in gene expression between two groups of astrocytes, including MerTK, which mediates synapse elimination, and Sparc, highly expressed in upper-layer astrocytes and deeper-layer astrocytes, along with Chrdl1 expressed at a higher level in upper-layer astrocytes than deeper-layer astrocytes (Bayraktar et al. 2020; Lanjakornsiripan et al. 2018).

Therefore, the majority of evidences point towards a complex picture of astrocytes also on a gene and protein level, which reflect their morphological heterogeneity, even within a single brain region. Astrocytes may share common genes, but then again variation in transcriptomes produces distinctive astrocyte subtypes, specialized in performing different functions.

Current astrocyte markers are either not homogeneously expressed in all astrocytes or do not entirely label the astrocyte soma and processes, hence, the importance of identifying the most appropriate combination of astrocyte markers in different brain regions in order to better guide researchers in exploring astrocyte functions.

Morphological Changes in Neuropsychiatric Disorders

Major Depressive Disorder

As mentioned before, astrocytes have different functions during development and in the adult CNS, in order to facilitate the formation of neural networks and maintain brain homeostasis. They act by providing nutrients and neurotrophic factors, by regulating ion and neurotransmitter homeostasis and by removing waste metabolites (Parpura et al. 2012). They are closely associated with neuronal synapses, forming the so-called tripartite synapse (Araque et al. 1999). With the endfeet of their processes, which wrap around synapses, they regulate the formation and refinement of neural circuits through complex events such as synaptogenesis, synaptic maturation, and pruning (Roman et al., 2020) (Bosworth and Allen 2017).

Most of the morphological studies in astrocytes have used immunohistochemistry techniques to label them with GFAP, a well-established marker for astrocytes, which make their identification relatively easy, although with the limitations described before (Williams et al. 2014). Among other methods, the Golgi staining and cresyl violet have been extensively used in neuroanatomical studies to show glial morphology (Chana et al. 2003; Torres-Platas et al. 2011).

Changes in astrocyte morphology, density, protein content, and gene expression have been described in a broad spectrum of neuropsychiatric disorders (Di Benedetto and Rupprecht 2013; Zhou et al. 2019). Findings from postmortem human brain

tissues have highlighted changes in glial cell morphology in mood disorders like major depressive disorder (MDD). Specifically, morphometric analysis revealed bigger glial cell nuclei, suggesting an enlargement of the glial cells which were located in the dorsolateral prefrontal cortex (dlPFC) of depressive patients (Rajkowska et al. 1999). In particular, 3-D reconstruction of gray and white matter astrocytes using Golgi staining revealed that fibrous astrocytes of the anterior cingulate cortex had bigger cell bodies, were more ramified, and presented longer lengths of their processes in depressed subjects who committed suicide, when compared to matched controls (Chana et al. 2003; Torres-Platas et al. 2011). Other evidences also suggested that changes occur in astrocyte volume in postmortem brain tissue of MDD patients in an age-dependent way, with older depressed patients (46–86 years old) showing larger astrocytes, when compared to their healthy age-matched controls, and younger depressed patients (30–45 years old) exhibiting smaller astrocyte areal fraction and packing densities when compared to their controls (Miguel-Hidalgo et al. 2000). However, no changes in glia clustering were found in the prefrontal area of postmortem brain tissue of MDD subjects, besides the reductions in glial cell densities (Cotter et al. 2002).

Astrocytes also play a role in establishing and modulating the integrity and functionality of the BBB, with astrocyte endfeet representing a major structural component of the BBB. In MDD, a decreased coverage of blood vessel walls by astrocytic endfeet positive for AQP4 ($AQP4^+$) was first described in 2013 (Rajkowska and Stockmeier 2013). The reduction reached a 50% level and was specifically restricted to the orbitofrontal gray matter of subjects with MDD, as compared to nonpsychiatric control subjects, but not in other brain areas. However, this effect was not accompanied by a similar difference when quantifying $GFAP^+$ astrocyte processes, suggesting a deficit related to AQP4 localization more than a simple structural impairment. Indeed, a functional impairment of the BBB, characterized by increased permeability, has been described in MDD, thereby supporting the idea that morpho-functional changes in astrocytes might strongly contribute to BBB dysfunctions (Rajkowska and Stockmeier 2013). In a similar way, Di Benedetto and colleagues confirmed a 60% reduction in coverage of blood vessels by AQP4 immunoreactive astrocyte endfeet in the adult prefrontal cortex (PFC) of high anxiety-like behavior rats (HAB), rats with an endogenous depressive-like phenotype, similar to the findings in MDD patients (Di Benedetto et al. 2016). Ex vivo and in vitro analysis additionally revealed that HAB astrocytes extend less processes than their control counterpart cells (Di Benedetto et al. 2016; Malik et al. 2020). Moreover, slightly different than in the human situation, GFAP staining additionally showed a more generalized lower morphological complexity of HAB astrocytes, when compared to control cells (nonselectively bred for anxiety behavior, NAB). Finally, antidepressant treatment with the commonly used antidepressant drug (AD) fluoxetine (FLX) increased the number of processes in healthy astrocytes, indicating this morphological change as a FLX pharmacological target. In addition, FLX restored the basal total number of processes per cell in HAB astrocytes, reversing the disease phenotype and suggesting such morphological changes as putative therapeutic targets of ADs (Fig. 3). However, the results showed that that the short-term treatment was not

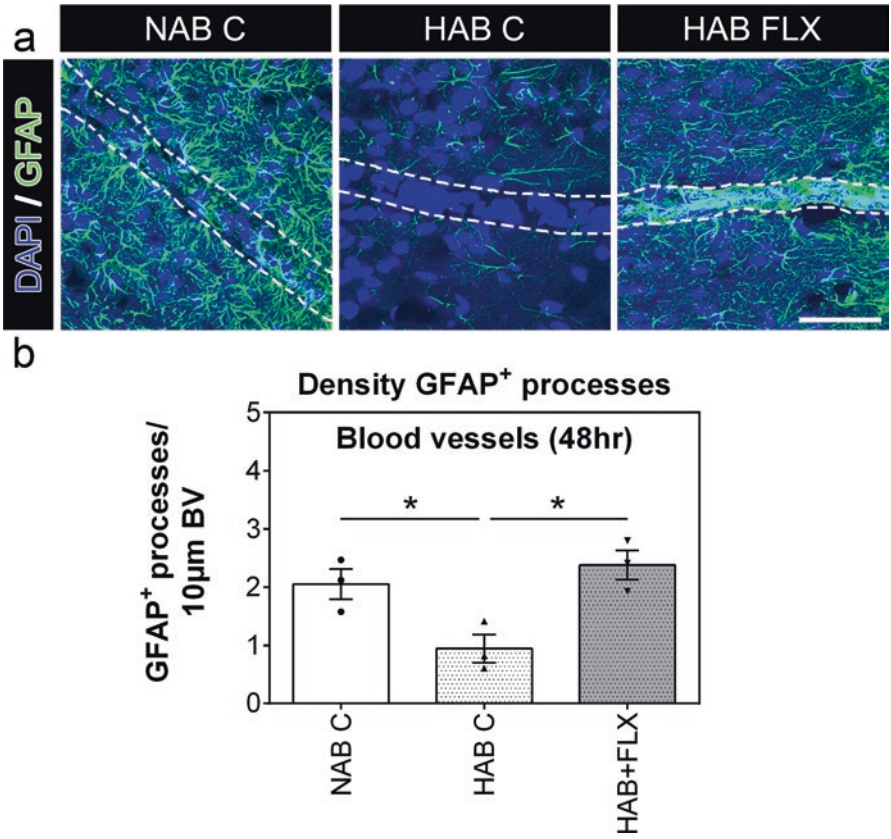

Fig. 3 Astroglia in MDD. (**a**) Representative photomicrographs of GFAP-stained brain slices from the PFC of NAB and HAB control (C) rats and HAB rats upon FLX treatment (HAB FLX). Stainings show a strong atrophy of GFAP$^+$ astrocytes in HAB brains, which could be rescued by short-term FLX treatment; (**b**) graph shows the quantification of GFAP$^+$ processes/10µm blood vessel (BV) and highlights the significant differences between NAB C/HAB C/HAB FLX. Data are presented as mean ± SEM, $^*p \leq 0.05$. Scale bar = 50µm

sufficient to relocate AQP4 to the astrocytic endfeet and rescue the coverage of blood vessels by AQP4+ processes, thus suggesting that long-term treatments might be necessary to reach a functional rescue, whereas short times may be sufficient to improve the structural deficits (Di Benedetto et al. 2016).

Our results about the role of astrocytes in mediating AD effects (Di Benedetto et al. 2013; Di Benedetto et al. 2016; Di Benedetto and Rupprecht 2013; Tanasic et al. 2016) become even more relevant when thinking about the ability of stress, a known trigger of neuropsychiatric disorders, to induce structural remodeling of astrocytes (Menard et al. 2017). Several findings from animal models have consistently showed that astrocytes change their morphology and physiological characteristics after they are exposed to particular psychological stressors. 3-D

reconstructions of astrocytes using high-resolution imaging methodologies highlighted profound changes in three main morphological parameters in GFAP$^+$ astrocytes from the PFC after chronic stress: astrocytes presented, in average, a ~40% reduction of process length, a ~56% decrease in process volume, and a ~58% decline in the number of process branches (Tynan et al. 2013). Interestingly, repeated chronic immobilization stress for 2 h/day for 10 consecutive days decreased the neuropil volume occupied by the astrocytes in the basal amygdala, but not in the CA3 area of the hippocampus. Measurements of neuropil volumes are relevant to map the physical extent of an association between astrocytes and neurons. Therefore, the changes found in the amygdala were interpreted as a reflection of a declined volume occupied by fine astrocytic protrusions, which are functionally interacting with neuronal structures (Naskar and Chattarji 2019).

Furthermore, using a chronic psychosocial stress paradigm for 5 weeks, it was found that this particular stress produced a 25% significant decrease in both the number and somal volume of astroglia in the hippocampus. These changes in astroglia plasticity correlated with the stress-induced hippocampal volume reduction observed in vivo and might account for hippocampal volume changes observed in the brains of patients suffering from neuropsychiatric disorders. Interestingly, FLX treatment prevented the stress-induced numerical decrease of astrocytes, but had no counteracting effect on somal volume shrinkage (Czeh et al. 2006; Czeh and Di Benedetto 2012). A similar finding was also described in C57/Bl6 mice after chronic treatment with corticosterone. Administration of 20 mg/kg of corticosterone once per day produced a significant decrease in number, somal volume, and process length of astrocytes in the hippocampus. This treatment additionally triggered a depressive-like behavior in male mice, accompanied by a decreased hippocampal volume, which may result from the abovementioned morphological changes associated with an impaired astrocyte branching complexity (Zhang et al. 2015).

Chronic mild unpredictable stress (CMUS) paradigm was also used in mice to induce stress-related reactions by using auditory and olfactory stimuli. Astrocytes in the hippocampal subfields were differently affected: those in the molecular layer were the mostly impaired, with a surface area which was significantly reduced in the CMUS-treated group, whereas CA1 and CA3 astrocytes were much less affected (Virmani et al. 2020). Interestingly, the same CMUS paradigm using different stressors, such as restricted space, exposure to overnight illumination, or food and water deprivations, did not significantly change the morphology of astrocytes in any hippocampal area. In any case, chronic treatment with the ADs FLX and imipramine promoted a transient reduction of astrocytic complexity after the 6-week protocol exposure to stress. However, those ADs facilitated restoration of the physiological astrocytic complexity when animals were re-exposed to stress, thus suggesting a protective effect of ADs to further potentially damaging conditions (Machado-Santos et al. 2019).

The examination of animal models of depression, such as the Flinders Sensitive Line (FSL) rats, a rat line selected for an endogenous depressive phenotype, showed a reduction in size of GFAP$^+$ astrocytes and in the branching patterns of astrocytic processes in the stratum radiatum of hippocampal area CA1. Moreover, astrocytes

in the molecular layer of the dentate gyrus (DG) were significantly smaller than their corresponding ones in the control group. Administration of ketamine, a drug with fast-acting AD effects, showed rapid and conspicuous rescuing effects on both parameters, the soma size and astrocyte arborization, in CA1 and DG areas (Ardalan et al. 2017).

In the stress-hyperresponsive Fischer rats, an early life isolation stress in pups produced a moderate but consistent reduction in the density of GFAP-immunoreactive astrocytes in areas implicated in both stress-related and depressive-like behaviors, such us the PFC, the CA1 and dorsal DG of the hippocampus, the cingulate cortex, and the amygdala (Leventopoulos et al. 2007). Another early life stress, namely, maternal deprivation, produced consequences in the postnatal (PN) development of rat pups (day PN15), with a reduction in astrocytic density and a shortening of astrocytic processes in the hippocampus, without affecting cell soma (Roque et al. 2016; Saavedra et al. 2017). Interestingly, no changes in astrocyte morphology have been reported related to long-term effects of maternal deprivation (Burke et al. 2013; Gondre-Lewis et al. 2016).

In an animal model of post-traumatic stress disorder (PTSD), induced by inescapable footshock, rats showed notable changes in hippocampal astrocytes, whereas astrocytes in the medial amygdala were left unaffected, when compared to controls. The astrocytic branching and number of primary processes were reduced in the lateral quadrants of the hippocampus in the PTSD group, with lateral quadrants defined as the portions of tissue parallel to the stratum pyramidale where astrocytes extend their processes. The analysis of the orientation index of astrocyte processes, determined by the quotient of the number of lateral intersections of the astrocytic processes divided by the number of their central intersections, indicated that PTSD model alters the polarity of hippocampal astrocytes, inducing a more fusiform shape (Saur et al. 2016).

In Rhesus macaques showing a self-injurious behavior (SIB), a complex neuropsychiatric condition characterized by a spectrum of abnormal neuropsychological and locomotor behaviors, astrocytic cell bodies in the white matter presented an atrophy, with significantly smaller cell bodies. Moreover, the total volume of astrocytic processes was significantly decreased in both white and gray matter astrocytes in the SIB group. Specifically, the astrocyte complexity was decreased in frontal cortical areas of SIB animals, with reduced numbers of bifurcations and process end points within the first 30μm radii around the cell body in both white and gray matter astrocytes. Finally, the total length of the cell arbor observed in white matter astrocytes was significantly decreased compared to controls. Sholl analysis is the most commonly used method in the previous studies. This type of analysis has been used to examine astrocyte and neuron arborizations. This method is appropriate to analyze the cell complexity, by quantifying the number of process branches and intersections and giving as a result branching profiles of dye-filled cells (Naskar and Chattarji 2019).

Schizophrenia and Bipolar Disorder

Interestingly, bigger nuclear sizes of glial cell seem to be specific of depressive disorders, with no change in nuclear glial sizes reported in schizophrenia (Rajkowska and Miguel-Hidalgo 2007). In one study, schizophrenic brains only present a trend increase in mean glial size in occipital areas 9 and 17 (Rajkowska et al. 1998). Another study in humans used electron microscopy to reveal ultrastructural abnormalities of astrocytes in the CA3 region of the hippocampus in young (<50 years old) and old (>50 years old) schizophrenic cases, with lower values of total area covered by the single astrocyte (Kolomeets and Uranova 2010).

A subgroup of patients with schizophrenia, which was included in the "high inflammatory" subgroup, was characterized by a prevalent occurrence of hypertrophic astrocytes with an associated higher expression of inflammatory markers, similar to results observed in rodent model of neuroinflammation (Catts et al. 2014).

In the white matter of brains from people suffering from schizophrenia and bipolar disorder, GFAP-labeled astrocytes exhibited significantly altered spatial cell distribution. Astrocytes were more clustered in the psychiatric groups than in the control group, suggesting that a disruption of a structural or metabolic support of axons might be among the triggers of the disease. This altered spatial distribution might depend on changes in astrocyte morphology, providing further evidence for the morphological abnormalities found in the white matter of schizophrenic patients (Hercher et al. 2014).

Data from the analysis of astrocytes in the subgenual cingulate cortex of schizophrenia patients have identified two types of astrocytes based on their morphology: fibrillary astrocytes, which were distinguished by multiple visibly stained processes, and gemistocytic astrocytes which presented larger cell bodies and either one or no stained processes. The study revealed an overall decrease in fibrillary astrocyte density in the cingulate white matter of patients, while gemistocytic astrocytes remained unaltered (Williams et al. 2014).

A study using glial progenitor cells derived from schizophrenic patients revealed alterations in the astrocytic phenotype, with specific deficits in both phenotypic maturation and differentiation processes. In this study glial progenitor cells (GPCs) produced from induced pluripotent stem cells (iPSCs) derived from patients with childhood-onset schizophrenia were further implanted into mice. The schizophrenia glial chimeras also showed delayed astrocytic differentiation and abnormal astrocytic morphologies. Sholl analysis of those chimeras further revealed that astrocytes derived from people suffering from schizophrenia had fewer primary processes, less proximal branching, longer distal fibers, and less coherent domain structure compared to the control-derived counterparts (Windrem et al. 2017). RNAseq also revealed a disrupted expression of genes associated with glial differentiation and synaptic development. For instance, the levels of neuroligins (NL)1, NL2, and NL3 have been found to be reduced in glial progenitor cells from schizophrenic patients when compared to controls (Windrem et al. 2017). Astrocytic

NL2 has been shown to control the balance of excitatory and inhibitory synaptic connections, as well as astrocytic NL1-3 has been seen to guide the establishment of astrocyte morphology. Silencing studies in transfecting astrocytes with short hairpin RNAs (shRNAs) against NL1-3 revealed that the neuron-induced astrocyte complexity in vitro was completely blocked. Those astrocytes were not able to develop the main branches during development at P7 and showed a delayed elaboration of their thinner processes into the neuropil by P21 with respect to control transfected astrocytes. Specifically, the knockdown of NL1 markedly reduced astrocytic neuropil infiltration volume at P7, which was reversed only later in development by P21. NL2 knockdown was much more severe, with a restricted volume infiltration at both time points. Conversely, silencing NL3 severely affected astrocyte growth only at P21. Moreover, silencing each individual astrocytic NL impaired astrocyte morphology by partially diminishing astrocyte arborization (Stogsdill et al. 2017).

Less is known, instead, about astrocytes in bipolar disorder. Histological studies of brains derived from people suffering from bipolar disorder have revealed alterations in the shape of the glial nucleus to a less rounded conformation in the dorsolateral prefrontal area 9 as well as a glial enlargement in layers I and III (Rajkowska et al. 2001).

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Part II
Astroglia in Mood Disorders

Astrocytes in Bipolar Disorder

Arthur M. Butt and Andrea D. Rivera

Introduction

Bipolar disorder (BD) is a complex group of neuropsychiatric disorders, typically comprising both manic and depressive episodes, termed bipolar I disorder, whilst manic attacks without depressive episodes are classified as bipolar II disorder (Carvalho et al. 2020). BD affects 1 in 100 people and approximately 45 million people worldwide, with a typical onset around the age of 20 years (McIntyre et al. 2020). The heritability of BD is high (≥70%) and genome-wide association studies (GWAS) have identified potential risk genes, although they have very small effect sizes (Gordovez and McMahon 2020). Genes consistently associated with BD include *Ank3*, an important scaffolding protein that anchors sodium channels essential for action potential generation at nodes of Ranvier and the axonal initial segment (Hughes et al. 2018; Ferreira et al. 2008), together with *Cacna1c* (Sklar et al. 2008; Ferreira et al. 2008), which encodes voltage-gated calcium channel Cav1.2 and supports evidence of altered calcium signalling being central to changes in synaptic function and plasticity in BD (Berridge 2014; Moon et al. 2018). In addition, BD is associated with major disruption of metabolism (Kato 2019) and circadian rhythms (Geoffroy et al. 2016; McClung 2007); multiple circadian gene associations have been identified, including *Clock, Gsk3b* and *Per2*, that are regulated by lithium treatment. Furthermore, neuroimaging and post-mortem studies consistently show altered glutamatergic signalling in BD, and the NMDAR antagonist ketamine is an effective anti-depressive and anti-suicidal treatment in BD (Li et al. 2018; De Sousa et al. 2017; Wilkowska et al. 2020). The underlying neuropathology

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of BD is not well established, but imaging and post-mortem studies have highlighted strong associations of BD with thinning of cortical grey matter (GM) and white matter (WM), with progressive atrophy being associated with more severe illness episodes, which is alleviated by lithium treatment (Hibar et al. 2018; Favre et al. 2019; Serafini et al. 2021; Passos et al. 2016). Cortical thinning is associated with the regional loss of neurones and astrocytes (Harrison et al. 2020; Peng et al. 2016). Astrocyte atrophy has major effects on synaptic signalling and plasticity, together with regulation of glutamate, calcium signalling, metabolism and sleep, all of which are disrupted in BD (Fig. 1) (Steardo Jr. et al. 2019; Peng et al. 2016). The gold standard treatment for BD remains the mood stabilizer lithium, together with valproic acid (VPA) and carbamazepine (CBZ) (Alda 2015; McIntyre et al. 2020; Carvalho et al. 2020). The therapeutic actions of lithium are due at least in part to its potent inhibition of glycogen synthase kinase 3β (GSK3β), both directly and indirectly by its activation of Akt, which inhibits GSK3β activity (Fig. 2) (Alda 2015). Inhibition of GSK3β and activation of Akt by lithium have been demonstrated in BD-relevant brain regions of the frontal cortex, striatum and hippocampus activity (Freland and Beaulieu 2012). At a cellular level, lithium is neuroprotective and, as the primary neuroprotective cells of the CNS, there is increasing evidence that astrocytes are prominently involved in BD and are therapeutic targets of lithium and other frontline and adjunct therapies in BD (Keshavarz 2017; Jia et al. 2018; Rivera and Butt 2019; Peng et al. 2016; Stenovec et al. 2020). In addition, genetic and

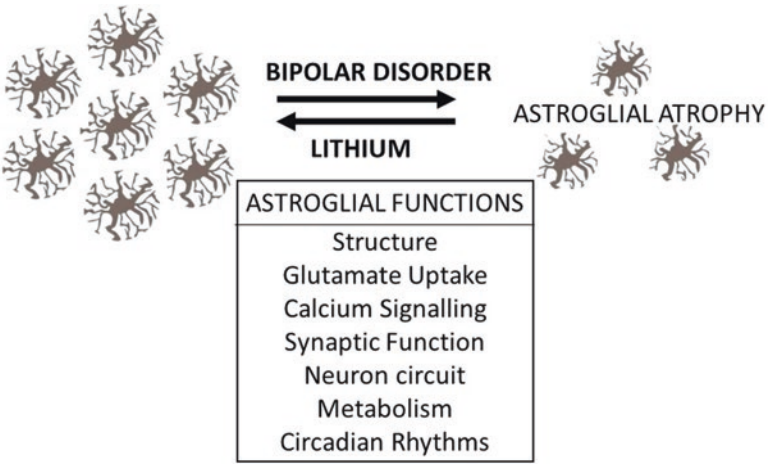

Fig. 1 Astrocyte atrophy and disruption of homeostatic functions in BD. Brain imaging and post-mortem studies consistently demonstrate decreased volume of grey matter (GM) and white matter (WM) in BD, due to astroglial atrophy and loss of specific neuronal populations. Astrocyte atrophy results in dysregulation of diverse astroglial functions, including structural changes, glutamate regulation, synaptic and neural circuit plasticity, together with metabolism and circadian rhythms, which are severely disrupted in BD. Notably, lithium has been shown to have positive effects on astroglial numbers, morphological plasticity and homeostatic functions, which underpin the protective effect of lithium on GM and WM thinning and its beneficial therapeutic effects in BD

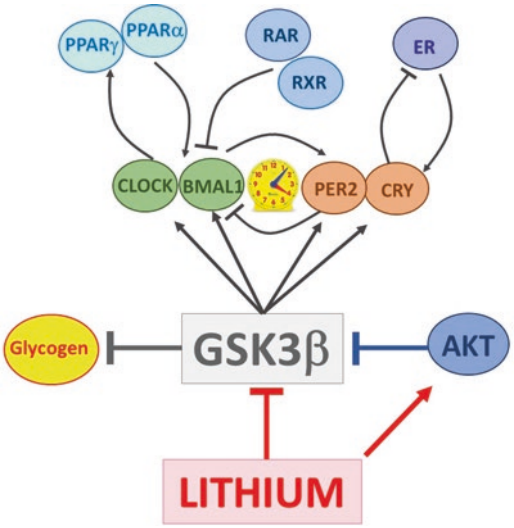

Fig. 2 GSK3β is a primary astroglial target of lithium in BD. GSK3β is a negative regulator of diverse cellular signalling pathways. Lithium is a potent inhibitor of GSK3β, both directly and indirectly by its activation of Akt, and this is a major factor in its beneficial therapeutic actions in BD. Astrocytes, like most cells, express an internal clock regulated by BMAL1/CLOCK and PER2/CRY and involving nuclear receptors (peroxisome proliferator-activated receptor gamma, PPAR; retinoic acid receptors, RAR/RXR; and estrogen receptors, ER), which are key BD-associated genes. Astrocytes are the main glycogen store in the brain and provide metabolic support to neurons via glycogenolysis and the astrocyte-neuron lactate shuttle; these astroglial functions are regulated by lithium via its actions on GSK3β, which inhibits the eponymous glycogen synthase. In addition to circadian rhythms and cellular metabolism, the cellular clock controls diverse astroglial functions that are severely disrupted in BD, including synaptogenesis

lithium-mediated inhibition of astroglial GSK3β has been shown to increase astroglial numbers in situ (Jung et al. 2016; Rivera and Butt 2019), consistent with the beneficial effects of lithium on attenuating thinning of GM and WM in BD. Notably, GSK3β is a master regulator of the circadian clock and cellular metabolism (Iitaka et al. 2005), which are disturbed in BD and are regulated lithium (Kato and Kato 2000; Geoffroy et al. 2014), and astrocytes play critical roles in maintaining circadian rhythms and brain energy balance (Niu et al. 2016; Brown and Ransom 2007; Brancaccio et al. 2019; Barca-Mayo et al. 2020). These studies demonstrate the importance of astrocytes in BD and highlight astroglial regulation of circadian rhythms and metabolism as major factors in the beneficial therapeutic effects of lithium in BD.

Neuropathology of BD

Although the results of BD neuropathology studies are variable, a consistent finding is the volume reduction of specific GM brain regions, such as the prefrontal cortex, and progressive changes have been associated with more severe illness episodes, which have been termed 'neuroprogression' (Serafini et al. 2021). The hypothesis is that a vicious cycle of repeated episodes results in the cumulative loss of neurones and glia, which in turn leads to further episodes and progressive brain atrophy and dysfunction. The importance of neuroprogression in BD remains controversial, and there is variability in the literature concerning regional GM atrophy in BD, most likely reflecting the heterogeneity of the disorder, as well as the impact of medication, whereby lithium may increase GM volume (Passos et al. 2016; Serafini et al. 2021). Nonetheless, brain imaging studies consistently demonstrate decreased volume of frontal, temporal and parietal GM in BD (Wang et al. 2020; Cotovio et al. 2020), and MRI analysis of 6503 individuals from the ENIGMA-BD Working Group found cortical GM thinning was associated with longer duration of illness and was alleviated by lithium treatment (Hibar et al. 2018). In addition, widespread white matter (WM) abnormalities are one of the most consistent findings in BD, for example as resolved by the ENIGMA-BD Working Group large cohort analysis of diffusion tensor imaging (DTI) data (Favre et al. 2019). Altered WM connectivity in frontocortical-striatal-thalamic circuits is most strongly associated with mood dysregulation in BD, and WM disruption is associated with a more severe course of illness (Lee et al. 2020; Mahon et al. 2010). A consistent feature of BD is shrinkage of the corpus callosum, the largest WM tract in the brain that connects the two cerebellar hemispheres, and these changes are associated with illness duration and are ameliorated by lithium treatment (Walterfang et al. 2009; Benedetti et al. 2013). Overall, the cognitive, behavioural, circadian and metabolic disturbances that characterize BD are associated with altered interconnectivity between brain regions. The balance of evidence indicates disease progression is associated with the loss of specific populations of neurones in several BD-relevant brain regions (Rajkowska et al. 2001; Bouras et al. 2001; Harrison et al. 2020; Mühleisen et al. 2014). However, BD is not characterized by neurodegeneration or neuroinflammation, and astrocyte reactivity or microglial activation are not characteristic features of BD (Giridharan et al. 2020; Harrison et al. 2020; Gigase et al. 2019). The most consistent finding in BD is astrocyte atrophy in specific cortical regions (Öngür et al. 1998; Rajkowska 2000; Toro et al. 2006; Hercher et al. 2014; Harrison et al. 2020), and associated dysregulation of astroglial homeostatic functions would have significant adverse effects on multiple aspects of BD neuropathology (Fig. 1).

Astrocyte Changes in BD

Recent systematic reviews highlight the variability of reports on astroglial changes in BD, depending on the brain regions analysed, and affected by differences in sample size and techniques used, as well as disease progression and medication (Giridharan et al. 2020; Gigase et al. 2019; Harrison et al. 2020). Nonetheless, it is evident that neurodegeneration, neuroinflammation and astrocyte 'reactivity' are not significant features of BD, the latter defined by increased density of cells (gliosis), cellular hypertrophy and increased expression of the astrocyte marker glial fibrillary acidic protein (GFAP) (Escartin et al. 2021). On the contrary, there is a consensus that cortical astrocytes are diminished in BD, both in numerical density and possibly morphological atrophy (Öngür et al. 1998; Rajkowska 2000; Hercher et al. 2014; Webster et al. 2005). These astroglial changes appear to be region specific, with decreased astrocyte density being a consistent feature of the prefrontal and cingulate cortex, as determined by Nissl staining (Todtenkopf et al. 2005; Öngür et al. 1998; Rajkowska et al. 2001), and by GFAP expression measured by immunostaining, immunoautoradiography and in situ hybridization (Hercher et al. 2014; Toro et al. 2006; Webster et al. 2005). The GFAP immunostaining area fraction was significantly decreased in BD (Hercher et al. 2014), indicating cellular atrophy, which has been reported in the ageing brain and a mouse model of Alzheimer's disease (AD) (Rodríguez et al. 2014). In contrast, no differences in astrocytes were evident in the amygdala, using Nissl staining and GFAP or S100β expression (Hamidi et al. 2004; Bezchlibnyk et al. 2007; Altshuler et al. 2010; Pantazopoulos et al. 2010). In the hippocampus, two studies using Nissl staining and GFAP immunolabelling found no changes in astrocytes (Malchow et al. 2015; Webster et al. 2001), whereas another study found S100β-immunopositive astrocytes were decreased in the hippocampus (Gos et al. 2013). Whilst recognizing that GFAP labels only a subset of astrocytes, and that there are multiple subtypes of GFAP-immunoreactive astrocytes in the human cortex (Verkhratsky et al. 2018; Escartin et al. 2021), the balance of evidence indicates that BD is associated with astrocyte atrophy in the prefrontal cortex, in particular the anterior cingulate cortex, which displays significant thinning in BD (Bouras et al. 2001). These studies are supported by transcriptomic analyses that revealed significant changes in astroglial genes in BD cortex (Ramaker et al. 2017; Toker et al. 2018), and changes in astrocytes may be present early in the illness course (Kaur et al. 2005). Overall, the observed astroglial atrophy is consistent with dysregulation of their homeostatic functions playing key roles in the clinical manifestations of BD (Fig. 1) (Peng et al. 2016).

Astroglial Glutamate Regulation in BD

Regulation of glutamate at synapses is a key function of astrocytes that is often altered in pathology (Escartin et al. 2021), and abnormalities in glutamatergic signalling are implicated in BD (Scotti-Muzzi et al. 2021; Li et al. 2018; De Sousa et al. 2017). GWAS studies associate glutamate signalling genes with BD (Nurnberger Jr. et al. 2014), and post-mortem studies have revealed reduced expression of NMDA, AMPA and KA glutamate receptors in BD (Beneyto and Meador-Woodruff 2008; Beneyto et al. 2007). Significantly, astrocyte atrophy in the prefrontal and anterior cingulate cortex correlates with abnormal glutamatergic activity in these regions in BD (Ongür et al. 2008; Eastwood and Harrison 2010). Astroglial reuptake of glutamate at synapses is via excitatory amino acid transporters (EAAT) 1 and 2 (encoded by the *SLC1A1/2* genes) and genetic variants of SLC1A2 are associated with BD (Fiorentino et al. 2015; Veldic et al. 2019). Furthermore, dysregulation of glutamate homeostasis in WM results in the loss of oligodendrocytes and myelin, resulting in WM thinning and disruption of connectivity that characterizes BD (Butt et al. 2014). The life-long generation of oligodendrocytes and myelin is the function of adult oligodendrocyte progenitor cells (OPCs), often called NG2-glia (Butt et al. 2002), and is essential for myelin repair (Ortiz et al. 2019), which is promoted by lithium treatment (Azim and Butt 2011). Glutamatergic signalling and neuronal activity drive OPC differentiation and myelination that is essential for learning and behaviour (Wake et al. 2011; Chen et al. 2018; Gibson et al. 2014; McKenzie et al. 2014; Xiao et al. 2016). Notably, disruption of OPCs has been shown to result in altered glutamatergic synaptic activity and to cause depressive-like behaviour in mice (Sakry et al. 2014; Birey et al. 2015), indicating the importance of bidirectional OPC-neuron interactions in cognitive function and behaviour (Rivera et al. 2016). Glutamatergic signalling in WM also stimulates oligodendrocyte-axon metabolic support, which is critical for maintaining WM connectivity (Rivera et al. 2021a), and pathological changes in oligodendrocytes and/or myelin ultimately lead to loss of axonal integrity and neuronal survival (Saab and Nave 2017), as observed in neuroprogression in BD. Hence, dysregulation of astroglial glutamate regulation has diverse negative effects on GM and WM function that would play major roles in the pathophysiology of BD.

Direct evidence of changes in astroglial glutamate regulation in BD is currently lacking. Expression levels of *SLC1A2*/EAAT2 mRNA in BD are largely unaltered in most studies (Medina et al. 2013; McCullumsmith and Meador-Woodruff 2002; Bernard et al. 2011; Zhang et al. 2021), and in one study, they were increased (Shao and Vawter 2008). Also, in BD prefrontal cortex where GFAP was reduced, Toro and colleagues observed no changes in glutamine synthetase (GS), the astroglial enzyme that recycles synaptic glutamate (Toro et al. 2006). In addition, a review of proton magnetic resonance spectroscopy (H-MRS) studies in BD failed to detect a significant correlation between lithium treatment and brain levels of glutamate, or of N-acetylaspartate (NAA), a marker for neuronal loss (Szulc et al. 2018). In contrast, VPA has been shown to increase mRNA and protein levels of EAAT1/2 and to

stimulate glutamate uptake in astrocytes (Johnson Jr. et al. 2018). Furthermore, drugs that target glutamate activity are promising adjunct therapies in BD, including the NMDA blocker ketamine and riluzole, which increase glutamate-glutamine cycling in BD (Diazgranados et al. 2010; Park et al. 2017; Sakurai et al. 2019; Brennan et al. 2010). Significantly, riluzole has been shown to increase astroglial *SLC1A2*/EAAT2 activity (Carbone et al. 2012), supporting its positive effects on glutamate cycling and depressive symptoms in BD. In addition, ketamine regulates astroglial cAMP signalling to attenuate their release of neurotransmitters (Stenovec et al. 2020). This is significant because cAMP signalling is dysregulated in BD (Dwivedi and Pandey 2008), and *ADCY2* (Adenylate Cyclase2, AC2), a key enzyme in cAMP signalling, has been identified as a risk factor in BD (Mühleisen et al. 2014), indicating the diverse effects of ketamine on astrocytes are therapeutically relevant to BD. Interestingly, treatment of astrocytes with VPA altered the excitatory-inhibitory balance in vitro by reducing synapse formation in inhibitory neurons (Takeda et al. 2021), which may be important in its mood-stabilizing effects in BD, although systematic analyses of H-MRS measurements of GABA in BD patients have been inconclusive (Schür et al. 2016). Thus, there is growing indirect evidence that altered astroglial glutamate regulation may play an important role in BD, and further studies are required to determine their importance in the pathophysiology and treatment responsiveness of this disorder.

Astrocytes and Disruption of Circadian Rhythms in BD

BD is characterized by marked disturbances in circadian rhythms, which are regulated by a master circadian pacemaker in the suprachiasmatic nuclei (SCN) of the ventral hypothalamus (Jagannath et al. 2013). The circadian clock consists of a transcription-translation negative feedback loop in which the transcription factors CLOCK and BMAL1 drive the expression of clock genes Period *(Per)* and Cryptochrome *(Cry)* that in turn feedback to regulate their own expression (Reppert and Weaver 2002). It is significant, therefore, that multiple circadian genes are associated with BD, including *Clock, Gsk3b* and *Per2* (McClung 2007; Akula et al. 2014). Moreover, lithium has been shown to affect behavioural and molecular circadian rhythms in humans and animal models, and the lithium response is associated with multiple circadian gene polymorphisms (Geoffroy et al. 2014). In addition to driving bodily circadian rhythms, most cells express an internal clock regulated by BMAL1/CLOCK which controls diverse cellular functions, including cellular metabolism, and changes in glucose are a particularly potent cue for cellular clocks, involving nuclear receptors that act as cellular nutrient sensors, including peroxisome proliferator-activated receptor gamma (PPAR-γ), retinoic acid receptors (RAR) and estrogen receptors (ER) (Li et al. 2013; Picard and Auwerx 2002). Genetic associations have been identified between lithium response and *PPARGC1A* and *RORA*, which are involved in both circadian rhythms and cellular metabolism (Geoffroy et al. 2016). Moreover, GSK3β is a master regulator of the circadian

clock and cellular metabolism (Iitaka et al. 2005), and synaptic plasticity of hippocampal neurones is dependent on GSK3β-mediated regulation of circadian rhythmicity (Besing et al. 2017), consistent with evidence that the cellular clock plays a key role in altered neuronal synaptic plasticity in BD (Vadnie and McClung 2017). Astrocytes possess functional circadian clocks that regulate their response to daily oscillations in brain activity and metabolism (McKee et al. 2020). Moreover, GSK3β is a direct target of lithium in astrocytes and acts at least in part to regulate PPAR-γ (Rivera and Butt 2019). Furthermore, astrocytes have been shown to autonomously sustain circadian patterns of neuronal activity in the SCN (Brancaccio et al. 2019), and astrocyte-specific deletion of *BMAL1* is sufficient to disrupt brain glucose homeostasis (Barca-Mayo et al. 2020). Overall, disruption of astroglial regulation of circadian rhythms and metabolism is likely to be a major factor in BD and in the beneficial therapeutic effects of lithium (Fig. 2).

Astrocytes and Altered Metabolism in BD

Abnormal metabolism is a consistent finding in BD (Kato and Kato 2000), and this strongly implicates astrocytes, which are key players in brain energy regulation. Astrocytes provide metabolic support to neurons via the astrocyte-neuron lactate shuttle, which is tightly regulated by neuronal activity (Hertz et al. 2006; Magistretti and Allaman 2018; Barros 2013). Astrocytes take up glucose via glucose transporters and store it as glycogen and pyruvate, which can be converted by lactate dehydrogenase 5 (LDH5) to lactate, that can be transferred via monocarboxylate transporters (MCTs) to neurons, where lactate is converted back to pyruvate by LDH1 and used for energy production. Notably, decreased glucose and elevated lactate in BD suggests a shift towards glycolysis (Dager et al. 2004; Hosokawa et al. 2009). Furthermore, lithium is a major inhibitor of GSK3β, which regulates cellular metabolism through glycogen synthase and pyruvate dehydrogenase (Jope 2011), and regulates glutamate metabolism and glycogen synthesis in the brain (Gould et al. 2004; Kohno et al. 2007) and in astrocytes (Fan et al. 2010; De Almeida Souza et al. 2010). Furthermore, treatment with lithium, CBZ or VPA has been shown to regulate GSK3β signalling and glycogen production in astrocytes (Jia et al. 2018). Notably, astrocytes also provide metabolic support for WM axons in the form of lactate (Niu et al. 2016; Brown and Ransom 2007) and provide glucose to oligodendrocytes, which in turn deliver lactate to axons via MCTs (Lee et al. 2012; Funfschilling et al. 2012). Disruption of astroglial or oligodendroglial axonal metabolic support results in altered axonal activity (Trevisiol et al. 2017), and ultimately a loss of axonal integrity (Alexandra et al. 2018). These studies emphasize that the role of astrocytes in altered metabolism and circadian rhythms in BD could underpin changes in GM and WM integrity and is an area of research that merits considerable attention.

Lithium-Responsive Astroglial Gene Networks

Lithium remains the main therapy for BD, and genomic analysis of the effects of lithium is considered crucially important for the identification of novel lithium-responsive genes in BD, as well as identifying pathophysiological mechanisms and therapeutic targets (Papiol et al. 2018). As noted above, lithium regulates multiple astroglial functions that are implicated in BD, but the mechanisms of actions are unresolved. To help fill this gap in our knowledge, we examined the effects of lithium in WM astrocytes, using a combined neurobiological and systems biological approach (Rivera and Butt 2019). A key finding was that the ECM-modifying enzyme Lysyl oxidase (LOX) was identified as a novel target of lithium that promotes astrocyte proliferation and profoundly affects their morphology, which is consistent with the positive effects of lithium in alleviating GM and WM thinning in BD. The structural role of astrocytes and their regulation of the ECM is essential for the maintenance and remodelling of synaptic and neural circuit function (Fig. 3), which are impaired when astrocytes undergo atrophy, as seen in ageing and pathology (Pirttimaki and Parri 2013; Sampedro-Piquero et al. 2014; Rodríguez et al. 2014). Hence, the identification of LOX as a BD-associated lithium-responsive astroglial gene that regulates astrocyte morphological remodelling requires further investigation to examine its role in astrocyte atrophy and its impact on neuronal circuit activity in BD, as well as developing new therapies that regulate LOX activity (Rivera and Butt 2019). Analysis of lithium-responsive astroglial genes revealed

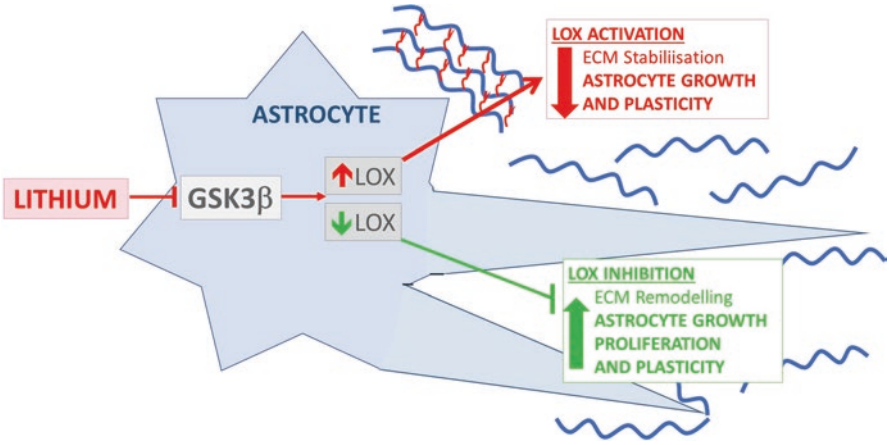

Fig. 3 Lysyl oxidase (LOX) is a novel target of lithium in astrocytes. Combined neurobiological and systems biology approaches identified the extracellular matrix (ECM)-modifying enzyme LOX as a major target of lithium in astrocytes (Rivera and Butt 2019). LOX activation promotes stabilization of the ECM to impede cellular growth and plasticity. Lithium inhibits LOX activity and increases astrocyte numbers and promotes morphological plasticity, which is essential for the maintenance and remodelling of synapses and neural circuity. These actions of astroglial LOX are consistent with the positive effects of lithium in rescuing astrocyte atrophy and GM/WM thinning in BD

up-regulation of neuron-supporting pathways that may be central to the positive therapeutic outcomes of lithium on rescuing GM and WM atrophy (Rivera and Butt 2019). Meta-analysis of BD-associated astroglial genes identified key genes with recognized importance in BD, including *Ank3, Cacna1, cAMP* and *Per2*, as well as multiple GluR and GABAR (Fig. 4). These analyses highlight diverse astroglial gene networks that are implicated in BD, including P2X7R that plays a role in depressive behaviour and has been suggested to have a role in BD in relation

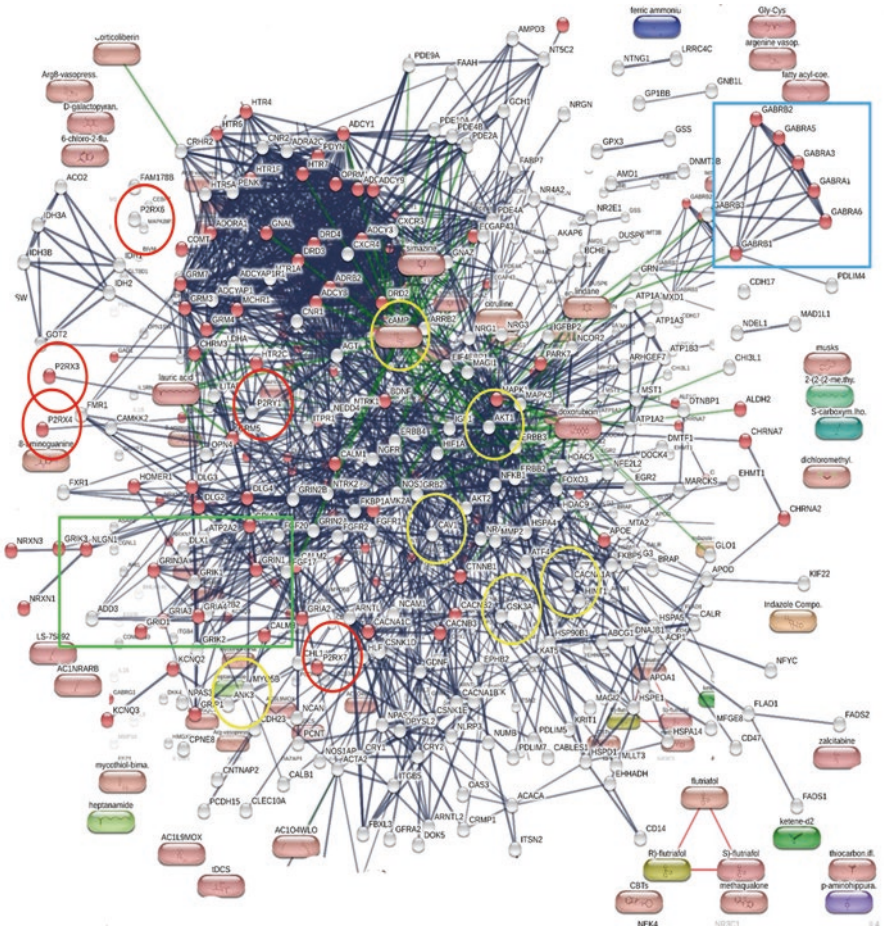

Fig. 4 BD-associated astroglial gene networks. Functional protein-protein network analysis of BD-associated astrocyte genes (Rivera and Butt 2019; Rivera et al. 2021b) resolved astroglial gene networks that have recognized importance in BD (highlighted in yellow circles, e.g. *Ank3*, *Cacna1*, *cAMP*, *Gsk3*), as well as multiple GluR (highlighted in green rectangle, e.g. *Grin1*, *Gria2*, *Grik3*), GABAR (highlighted in blue rectangle, e.g. *Gabra1*, *Gabrab1*) and P2R (highlighted in red circles, e.g. *P2ry1*, *P2rx3 P2rx7*). Many of these gene networks are involved in neuron-astrocyte signalling and regulation of cellular metabolism, which have important implications for BD

inflammation (Illes et al. 2020). In addition, P2X7R has a well-established role in astroglial calcium signalling and release of neurotransmitters (Butt 2011; Hamilton et al. 2008) and regulation of cellular metabolism (Rivera et al. 2021a), which have important implications for BD (De Sousa et al. 2017). Pharmacogenomic analysis identified pioglitazone and flavanols as small molecules that target BD-associated lithium-responsive astroglial genes (Rivera and Butt 2019), which is of interest because piogliatazone acts on PPAR-γ, whilst flavanols activate ER (De Almeida et al. 2020; Rivera and Butt 2019), which are integral to regulation of circadian rhythms and metabolism and are dysregulated in BD. Notably, pioglitazone has been shown to have promising results for its anti-depressant activity in clinical studies (Nierenberg et al. 2018; Brusotti et al. 2017), and flavanols have been shown to have positive effects in anxiety, mood disorder, and cognitive decline in animal models (Stringer et al. 2015; Wang et al. 2012). These combined neurobiological and pharmacogenomic strategies are beginning to identify novel astroglial targets that are promising therapies in BD.

Conclusions

To date, the neuropathology of BD has not been fully defined, but a consistent replicated finding is that cortical thickness is significantly decreased in BD and is associated with loss of astrocytes and subpopulations of neurons. An important negative finding is that astrocyte reactive gliosis and neuroinflammation are not major features of BD. The effects of lithium and other treatments have provided further evidence that disruption of astroglial homeostatic functions is of primary importance in BD neuropathology. These studies highlight the importance of GSK3β in astroglial regulation of circadian rhythms and metabolism in BD. Moreover, BD is highly specific in its response to lithium, and lithium-responsive astroglial gene networks have a distinct signature that provides an insight into the beneficial therapeutic effects of lithium in BD. Astrocytes are important therapeutic targets in BD, highlighting the critical need for further research into specific astrocyte-neuron interactions that are dysregulated in BD.

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Astroglia Abnormalities in Post-stroke Mood Disorders

Tracey Singer, Sarah Ding, and Shinghua Ding

Overview of Stroke

Stroke is the leading cause of serious, long-term disability in the USA. Stroke can be categorized into two different types—ischemic stroke and hemorrhagic stroke. According to a recent report from American Heart Association (AHA), of all the strokes in the USA, 87% are considered ischemic stroke, 10% are intracerebral hemorrhage (ICH), and 3% are subarachnoid hemorrhage (SAH) (Virani et al. 2020).

Ischemic stroke occurs when the brain's blood vessels become narrowed or blocked (Moskowitz et al. 2010). This is problematic for the brain because it depends on arteries to carry fresh blood to it in order to bring in oxygen and glucose (as well as other nutrients) and remove carbon dioxide and cellular waste. If the arteries are blocked for too long, neurons, the most important cell type in central nervous system (CNS), cannot produce enough energy and will stop functioning and die. Ischemic stroke is most often caused by atherosclerosis, which is the buildup of fats, cholesterol, calcium, and other substances called plaque on artery walls (Campbell et al. 2019; Moskowitz et al. 2010; Lo et al. 2003). Atherosclerosis is a progressive disease and begins with damage to the inner layer of an artery. Over time, the plaque will harden, and arteries will become narrower, limiting blood flow and eventually forming blood clots, further narrowing arteries and limiting the flow of oxygen-rich blood. A blood clot may completely block blood flow or break apart and trigger a stroke. Although the cause of atherosclerosis is not known, factors

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such as high blood pressure, high cholesterol, obesity, diabetes, and tobacco may increase risk for the disease.

Ischemic stroke can be further categorized into thrombotic stroke and embolic stroke (Barber and Demchuk 2003; Dirnagl et al. 1999). Thrombotic stroke, or cerebral thrombosis, is caused by a blood clot (thrombus) that blocks blood flow in a damaged cerebral artery leading to or within the brain. Large-vessel thrombosis occurs when arteries such as the carotid or middle cerebral are blocked, and small-vessel thrombosis occurs when the brain's smaller, yet deeper, penetrating arteries are blocked. Embolic stroke, or cerebral embolism, is caused by a wandering blood clot (embolus) in an artery somewhere other than the brain such as the neck or heart. The bloodstream carries the clot, which blocks a blood vessel in or leading to the brain (embolism). Again, this restricts the flow of blood to the brain and results in near-immediate physical and neurological problems. The main cause of embolism is atrial fibrillation, an irregular heartbeat which has the potential to develop blood clots within the heart. These clots can then circulate to the brain, causing ischemic stroke. The risk of stroke from atrial fibrillation depends on many factors including age, high blood pressure, and diabetes.

Hemorrhagic stroke, on the other hand, is caused by the leaking or bursting of blood vessels (Moskowitz et al. 2010). The leaked blood from vessels in the brain puts pressure on brain cells and damages them. Hemorrhagic strokes can be a result of conditions affecting blood vessels, including high blood pressure, overtreatment of blood thinners, aneurysms, trauma, cerebral amyloid angiopathy (protein deposits in blood vessel walls that weaken vessel walls), and arteriovenous malformation (the rupture of an abnormal tangle of thin-walled blood vessels). Intracerebral hemorrhage is the most common type of hemorrhagic stroke, occurring when brain arteries burst and flood surrounding tissue with blood. Subarachnoid hemorrhage refers to bleeding in the subarachnoid space, which is the area between the brain and tissues that surround the brain.

There are a number of detectable clinical symptoms and pre-stroke warning signs (Saengsuwan et al. 2017; Mochari-Greenberger et al. 2014) including sudden unilateral weakness (paralysis of face, arm, or leg on one side of the body), sudden trouble with speaking and understanding speech, sudden trouble with walking, loss of balance, sudden blackened or blurred vision in one or both eyes, double vision, and sudden and severe headaches perhaps accompanied by vomiting, dizziness, or altered consciousness. These symptoms are dependent on which side and region of the brain are affected and how severely the brain is damaged. It is often the case that only one side of the body is affected.

After a stroke, some patients will recover fully, others will be disabled long term or for the rest of their lives, and some will die if the damage to their brain is too severe. Approximately 3% of males and 2% of females reported that they were disabled because of stroke (Virani et al. 2020). Some problems that patients may experience after stroke can be managed by medical professionals through different types of rehabilitation therapy (Campbell et al. 2019). Regaining the activities of daily living become the focus of rehabilitation after stroke. For stroke survivors, the first 3 months post stroke are the most important period for recovery and when patients

show the most improvement (Grefkes and Fink 2020; Ronning and Guldvog 1998; Poulin et al. 2016). The goal of rehabilitation is to restore function as close as possible to "normal" or find strategies to work around new limitations. For example, speech therapy can help those who have trouble understanding or producing speech. Physical therapy helps with relearning movement and coordination skills lost after stroke which may include paralysis and/or weakness on one or both sides of the body. Occupational therapy improves daily activities such as eating, drinking, dressing, bathing, reading, and writing. Stroke patients may have trouble with chewing and swallowing or bladder and bowel control, so occupational therapists may also help them regain these skills. Even though rehabilitation psychologists and neuropsychologists can help, many patients still suffer long-term complications (effects). These complications are not only physical symptoms such as weakness, paralysis, difficulty swallowing, gait instability, and falls and fractures but also pain syndromes, depression, anxiety, pseudobulbar affect, epilepsy, cognitive impairment, and dementia (Virani et al. 2020).

Stroke has a large impact on public health and significant financial costs. A comprehensive study was conducted on 97,374 hospitalizations with a primary or secondary diagnosis of stroke from 2006 to 2008. It found that ischemic, hemorrhagic, and other types of strokes had average hospitalization costs of $18,963, $32,035, and $19,248, respectively. Overall, hemorrhagic stroke cost $14,499 more than ischemic stroke. In addition, the direct medical cost of stroke in 2008 in the USA was estimated to be $18.8 billion, and for the same year, the estimated per-person expenditure for stroke care was $7657 (Wang et al. 2014a). These costs largely increased based on the 2020 update of Heart Disease and Stroke Statistics from America Heart Association (AHA). According to the update, the average annual direct medical cost of stroke in the USA was $28.0 billion and direct care was estimated at $7902 in 2014 and 2015 (Virani et al. 2020). The costs of hospitalizations involving stroke are high and vary greatly by type of stroke, diagnosis status, and comorbidities.

In this chapter, before briefly describing the pathological processes of ischemic stroke, we will focus on the role of astrocytes in post-stroke mood disorders.

Pathological Processes of Ischemic Stroke

Acute Responses and Cell Death After Ischemic Stroke

Healthy brain tissue has a high level of consumption of oxygen and glucose. Neuronal function relies on continuous ATP production which requires oxygen and glucose from the blood. When a focal ischemia stroke takes place, cerebral blood flow is less than 20% of the normal standard at the ischemic core (IC) (Dirnagl et al. 1999; Lo et al. 2003). Impairment of cerebral blood flow restricts delivery of

glucose and oxygen, impairing the energetics required for ion gradients and leading to a loss of membrane potential in glia and neurons.

In focal ischemic stroke (FIS), the regions determine the pattern of cell death. Necrosis occurs in the IC in the acute phase, causing irreversible tissue loss while apoptosis occurs in the penumbra or peri-infarct region (PIR), which is a region between the lethally damaged IC and the normal brain. The PIR has partially preserved energy metabolism (moderately hypo-perfused) and retains structural integrity but has lost or impaired function. While cells in the IC can undergo permanent anoxic depolarization, cells in the PIR can repolarize with more energy consumption. This region can progress to infarction due to persistent excitotoxicity, spreading depolarization, inflammation, and apoptosis (Dirnagl et al. 1999). Therefore, the goal of neuroprotection is to salvage the ischemic penumbra. Alternative blood flow pathways, called collaterals, can sustain viability in penumbral regions, although the extent of collateral flow varies between individuals (Dirnagl et al. 1999). Patients with good collateral blood flow have infarcts that progress slower, while those with poor collateral blood flow display a more rapid progression of infarction.

Anoxic depolarization develops minutes after ischemia in neurons. As a result of the loss of membrane potential, voltage-dependent Ca^{2+} channels are activated, and excitatory amino acids, including glutamate, are released into the extracellular space (Campbell et al. 2019; Lo et al. 2003). Since energy-dependent reuptake is impeded, glutamate accumulation in the extracellular space is exacerbated. *N*-methyl-D-aspartate receptors (NMDARs) are blocked by extracellular Mg^{2+} under normal conditions; however, upon depolarization, the Mg^{2+} is removed, which leads to substantially higher conduction (Nowak et al. 1984) and subsequent Ca^{2+} influx and release from intracellular stores (Soriano et al. 2008; Wu and Tymianski 2018; Mayer and Miller 1990). Glutamate accumulation and subsequent Ca^{2+} overloading have diverse consequences. Ca^{2+} overloading in neurons following bioenergetic failure activates numerous Ca^{2+}-dependent enzymatic reactions and subsequently induces lipolysis, proteolysis, breakdown of ion homeostasis, and disaggregation of microtubules, causing cell death and tissue damage in the IC during acute phase after ischemic stroke (Folbergrova et al. 1995). The Ca^{2+} increase also activates neuronal nitric oxide synthase (NOS) and results in free radical production and cell death processes such as apoptosis, necrosis, necroptosis, and autophagy. NO reacts with a superoxide anion to form peroxynitrite that promotes tissue damage due to its highly reactive nature (Iadecola et al. 1997; Barber and Demchuk 2003). Additionally, the activation of phospholipase A_2 and cyclooxygenase generates free-radical species leading to lipid peroxidation and membrane damage. An increase in free radicals leads to a leaky mitochondrial membrane and subsequent cytochrome C release, which triggers apoptosis. Studies have shown that mice whose iNOS gene expression was induced with mRNA had larger infarcts and motor deficits produced by occlusion compared to iNOS knockout mice (Iadecola et al. 1997).

Ca^{2+} increase was also observed in astrocytes in the acute phase following FIS. It was reported that astrocytes exhibited enhanced Ca^{2+} signaling in IC and PIR after photothrombosis (Ding et al. 2009), which may in turn induce more glutamate

release from astrocytes. Deletion of IP_3R2 in astrocytes could reduce brain infarction and limit motor function deficits (Li et al. 2015; Dong et al. 2013). These results suggest that, in addition to neuronal Ca^{2+} signaling, astrocytic Ca^{2+} increase also contributes to brain damage through a non-cell autonomous effect.

There are two major modes of ischemic cell death: necrotic and apoptotic. Necrosis only occurs after exogenous insults. Following acute, permanent vascular occlusion, necrosis is the predominant form of cell death taking place in the IC, where the cells shrink and become very electron-dense (Lipton 1999). A hallmark of necrosis is the double-stranded breakdown of DNA into nucleosomal segments, which manifests as DNA laddering with fragments that are multiples of around 200 bp (Bonfoco 1995; Orrenius 1995). Overactivation of poly(ADP-ribose) polymerase (PARP), an NAD^+-consuming enzyme, has been proposed to lead to necrosis by excessive energy loss (Eliasson et al. 1997; Yuan 2009). Deletion of PARP-1 or use of PARP-1 inhibitors is neuroprotective in vitro and in vivo following ischemia (Eliasson et al. 1997; Zhang et al. 1994). Calpain is a cytosolic Ca^{2+}-activated protease and is known to be highly upregulated after ischemia (Vosler et al. 2011; Bano et al. 2005). Its activation from Ca^{2+} overloading under ischemic conditions contributes to neuronal cell death by cleaving multiple substrates such as cytoskeletal and associated proteins, kinases, phosphatases, membrane receptors, and transporters. Group I mGluR inhibitors 2-methyl-6-(phenylethynyl)pyridine (MPEP) and LY36738 could inhibit chaplain activation and thus reduce brain infarction (Li et al. 2013a).

Different from the necrotic death in the IC, neurons in the PIR may undergo apoptosis several hours or days after the onset of ischemic stroke. The protein families of Bcl-2 and caspase play critical roles in the activation, signal transduction, and execution of apoptosis (Broughton et al. 2009; Yuan 2009). Among the identified caspases, caspases 1, 8, and 9 appear to have key roles in ischemia-related apoptosis (Broughton et al. 2009; Yuan 2009). Caspases are activated when cytochrome C is released from the mitochondria and activates an apoptosome complex in the presence of dATP (Broughton et al. 2009). Activated caspases are aspartate-specific cysteine proteases that cleave enzymes and modify proteins which affect homeostasis and repair. Caspase activity can be blocked by the administration of small peptides which bind covalently to the catalytic pocket and alkylate the cysteine at position 70. Caspase inhibitors have been shown to decrease the volume of dead tissue in ischemia as well as neurological deficits (Hara et al. 1997). When ischemia is mild, inhibitors are particularly effective since they can be coupled with MK801, an NMDA-receptor antagonist, or growth hormones like fibroblast growth factor. While NMDA-receptor antagonists are typically administered before or immediately after ischemia, caspase inhibitors may still reduce injury even when injected many hours later. TNF1α, a cytokine, is also involved in apoptosis. TNF1α can exacerbate injury by causing a rapid decrease in mitochondrial membrane potential and thus impair mitochondrial function and increase caspase 8 activity, resulting in the release of cytochrome c from the mitochondria (Doll et al. 2015). Apoptosis-inducing factor (AIF) translocation from mitochondria to nuclei is involved in caspase-independent apoptosis (Wang et al. 2016; Broughton et al. 2009). NAD^+

repletion or neuronal overexpression of NAMPT, the rate-limiting enzyme in the NAD^+ salvage pathway, can reduce glutamate- and OGD-induced apoptosis through suppressing AIF translocation (Wang et al. 2014b, 2016). It is worth mentioning that one insult may lead to more than one mode of death in the same cell population, and cells may also manifest signs of multiple forms of death (Wang et al. 2016).

Astrocytes and Reactive Astrogliosis After Ischemic Stroke

Astrocytes are starlike cells and the most abundant glial cell type in the CNS. Classically, based on morphology and specific protein markers, there are two major types of astrocytes in the adult brain: fibrous astrocytes, present in white matter tracts such as the corpus callosum, and protoplasmic astrocytes, present in gray matter such as the cortex. Mature astrocytes have the following eight criteria (Kimelberg 2010): (a) electrically non-excitable; (b) a very negative membrane potential determined by the transmembrane K^+ gradient; (c) expression of functional transporters for glutamate and GABA uptake; (d) a large number of intermediate filament bundles, which are the sites of the astrocyte-specific protein glial fibrillary acidic protein (GFAP); (e) having glycogen granules; (f) processes from each cell surrounding blood vessels; (g) many more processes from each cell surrounding synapses; and (h) linkage to other astrocytes by gap junctions consisting of connexins (CX) 43 and 30.

Astrocytes are traditionally considered as supporting cells for maintaining ionic homeostasis and providing growth factors for neurons and structural support in the CNS. Protoplasmic astrocytes exhibit the following functions under normal conditions (Kimelberg and Nedergaard 2010; Kimelberg 2010): (a) extracellular K^+ buffering, (b) control of extracellular H^+ and brain pH, (c) uptake of glutamate and GABA with their transporters, (d) mobilizing intracellular Ca^{2+} stores by activation of G-protein-coupled receptors (GPCRs) such as mGLuR5 and P2Y, (e) regulation of cerebral blood flow, (f) control of water transport by aquaporin (AQP) water channel, (g) astrocyte-neuron lactate shuttle, and (h) modulation and control of synaptic activity.

Although many astrocytes conform to the aforementioned criteria and functional roles, they are heterogeneous in morphology, molecular expression, and physiological function (Zhang and Barres 2010; Matyash and Kettenmann 2010). Morphologically, a protoplasmic astrocyte is highly branched and has several primary processes each with elaborated sub-branched fine process arborizations to form a bush-like territory with little overlap between neighboring astrocytes (Wilhelmsson et al. 2006; Bushong et al. 2002). A fibrous astrocyte has thicker and less branched processes with a high degree of overlap with neighboring astrocytes. Intermediate filament protein GFAP is primarily expressed in the thick main processes in astrocytes and has been considered as a “pan-astrocyte” marker. Transcriptomic study has revealed that the Aldh1L1 gene is the most widely and homogeneously expressed in astrocytes and that the Aldh1L1 protein is highly

expressed in the cell body and extensive processes of an astrocyte (Cahoy et al. 2008). Therefore, Aldh1L1 is now considered as a new "pan-astrocyte" marker. Growing evidence indicates that astrocytes also play an active role through the "tripartite synapse," which includes the pre- and post-synaptic neuron as well as the surrounding astrocyte. Astrocytes can modulate synaptic function, wakefulness, cognition, and memory (Araque et al. 1999; Halassa et al. 2007, 2009; Haydon 2001; Volterra and Meldolesi 2005; Khakh and Sofroniew 2015; Santello et al. 2019; Cui et al. 2018; Suzuki et al. 2011). Therefore, astrocytes are global controllers in the CNS which coordinate both local responses and those over larger distances.

Astrocytes are also involved in neurological disorders, including ischemic stroke (Seifert et al. 2006; Nedergaard and Dirnagl 2005; Maragakis and Rothstein 2006; Ding et al. 2009; Choudhury and Ding 2016; Ding 2014; Li et al. 2015). Ischemia induces a variety of molecular and cellular changes in astrocytes at the PIR, including cellular proliferation, morphology, and gene expression in a temporally and spatially dependent manner. Reactive astrogliosis and subsequent formation of a glial scar are the hallmarks of focal ischemic stroke (Lo 2008; Choudhury and Ding 2016; Ding 2014). The activated astrocytes are therefore called reactive astrocytes (RAs) that can be detected by enhanced expression of GFAP and many other proteins, as well as dramatic morphological changes (Choudhury and Ding 2016; Li et al. 2014; Sofroniew and Vinters 2010).

RAs in the PIR exhibit spatiotemporally dependent changes in morphology (hypotrophy), proliferation capacity, function, and gene expression during the subacute phase (Barreto et al. 2011; Li et al. 2014; Choudhury and Ding 2016). Morphologically, RAs become hypertrophic with large processes that can be revealed by GFAP staining. After a prolonged time following focal ischemic stroke, the morphology of RAs remains stable, the proliferation of RAs ceases, and a glial scar is formed (Barreto et al. 2011; Li et al. 2014; Ding 2014; Choudhury and Ding 2016; Burda and Sofroniew 2014; Voskuhl et al. 2009). Reactive astrogliosis and glial scar formation eventually cause substantial tissue remodeling and permanent structural changes in the penumbra. Analysis of immunostaining for GFAP and individually dyed cells in astrogliosis induced in the cortex or hippocampus by electrically induced lesion revealed that astrocyte processes become thicker and bushier (Wilhelmsson et al. 2006; Li et al. 2014; Zhang et al. 2020b).

The developing scar contains extracellular matrix components, and this extracellular proteoglycan deposition is part of the initial response that likely limits the spread of damage. The scar narrows as it matures, but persisting features remain, such as the upregulation of GFAP in astrocytes and their tightly intertwined processes. Selective impairment of scar formation leads to a greater spread of tissue damage and worse neurological outcomes. The impaired restoration of the blood-brain barrier leads to greater infiltration of leukocytes, inflammatory cell spread, and increased neuronal loss, which were observed when features of glial scar maturation were disrupted by transcription 3 (STAT3) in astrocytes (Wanner et al. 2013). Treatment with DAPT, which inhibits the Notch-activating enzyme γ -secretase, reduces damage to the ischemic brain, possibly by causing a reduction in the

proliferation of reactive astrocytes. From this treatment or conditional knockout of the receptor, mice with impaired Notch signaling exhibited more microglia and macrophage invasion (Shimada et al. 2011; LeComte et al. 2015). It has been suggested that proliferation and differentiation of reactive astrocytes is promoted by Notch signaling via the translocation of the transcription factor Olig2 from the cytosol to the nucleus (LeComte et al. 2015).

On the other hand, the proliferation rate reaches a peak 3–4 days after FIS and recedes thereafter (Li et al. 2014; Barreto et al. 2011). Thus, metabolically, RAs are highly active on day 3–4 post-stroke to meet high energetic and biosynthetic demands for proliferation. Proliferation of RAs occurs mostly within 200μm from the IC and allows for the development of a glial scar after ischemia (Choudhury and Ding 2016; Zhang et al. 2020b; Li et al. 2014). Some astrocytes in the tissue adjacent to the infarct are actually derived from neural stem cells which migrate from the subventricular zone, and some survive as a part of the mature glial scar weeks after stroke (Faiz et al. 2015). Other cells, including microglia and/or macrophages, peri-vascular pericytes, or stromal cells, also proliferate (Barreto et al. 2011; Li et al. 2014; Fernandez-Klett et al. 2012). Many signaling pathways, including mitogen-activated protein kinases (MAPK), Notch signaling pathway, STAT3, and transforming growth factor beta (TGF-β) signaling, may participate reactive astrogliosis after ischemic stroke (Choudhury and Ding 2016).

Most changes in gene expression in RAs are due to altered cellular responses in the PIR, based on gene array analysis of RAs acutely isolated from brain tissue following MCA occlusion (Zamanian et al. 2012). For many genes, increased expression peaked 1 to 3 days after the onset of stroke, while a small proportion of genes including GFAP and some chemokines had increasing expression up to 1 week after stroke. Evidence also suggests that astroglia are influenced by specific conditions associated with the insult rather than an all-or-none response (Zamanian et al. 2012).

RAs have been demonstrated to have protective effects after FIS and injury (Linnerbauer and Rothhammer 2020; Myer et al. 2006; Faulkner et al. 2004; Anderson et al. 2016; Choudhury and Ding 2016). Proliferating RAs may impact tissue preservation, repair/remodeling, and functional outcome. Recent studies indicate RAs are also involved in depression, anxiety, cognition, and post-stroke mood shifting.

Post-stroke Symptoms and Post-stroke Mood Disorder (PSMD)

Mood disturbances are also frequent symptoms in stroke survivors (Kim 2016). After a stroke, many patients not only have some physical disability including difficulties in moving, speaking, and seeing, but it is common that patients may also exhibit changes in mood or emotion even after rehabilitation therapy (Schottke and Giabbiconi 2015). Anger, frustration, lack of motivation, and crying or laughing for

the wrong reasons are also common for stroke patients. Post-stroke depression (PSD) (Robinson and Jorge 2015), post-stroke anxiety (PSA) (Maaijwee et al. 2016), and pseudobulbar affect (PBA) (Gillespie et al. 2016) are common post-stroke mood disorders (PSMD).

Symptoms of PSD include depressed mood, anhedonia, loss of energy, decreased concentration, and psychic retardation. It is characterized by feelings of overarching sadness, lack of pleasure, or changes in eating and sleeping patterns. Multiple studies have found that PSD affects between one-third to two-thirds of stroke survivors (Schottke and Giabbiconi 2015; Fang et al. 2017; Ayerbe et al. 2013; Kim 2016; Robinson and Jorge 2015; Virani et al. 2020), although its prevalence decreases over time. A systematic review of patients found that depression is associated with increased disability and mortality (Ayerbe et al. 2013).

PSA affects about 20% of survivors and occurs when they focus on worries and feel anxious for no particular reason (Schottke and Giabbiconi 2015; Wright et al. 2017). The core symptoms of PSA are excessive anxiousness or worry and difficulty in controlling worries, restlessness, decreased energy, poor concentration, irritation, nervous tension, and insomnia (Maaijwee et al. 2016). Meta-analyses have suggested that there is a significant correlation between PSD and PSA (Schottke and Giabbiconi 2015; Wright et al. 2017).

PBA is characterized by a mismatch between feelings and expression. Individuals may cry or laugh in an uncontrolled manner. Crying is a more common PBA presentation following stroke than laughing (Gillespie et al. 2016). PBA affects approximately one in five stroke survivors at the acute and post-acute phases and one in eighth survivors 6 months or more post-stroke. Research indicates that PBA is more common in survivors of brainstem stroke, but it can also occur with other types of strokes (Balakrishnan and Rosen 2008).

Tools for cognitive and mood assessment have been suggested (Quinn et al. 2018). A framework for assessment emphasizes the need for differing approaches to testing at differing points in the stroke pathway rather than a comprehensive critique of all cognitive and mood assessment tools. Cognitive and mood problems are both associated with poor outcomes of stroke. Clinically, a number of drug and psychosocial treatments have been assessed, but the results have been disappointing. These drug trials are generally of poor quality and do not provide sufficient information to judge their true costs and benefits (Hackett et al. 2008). Psychosocial interventions are popular with patients, but there is conflicting evidence for their effectiveness in either treating or preventing anxiety and depression (Gao et al. 2016; Wu et al. 2012). The problem-based and behavioral therapies seem to be promising for patients with stroke (Hill et al. 2019). Improved coping skills should result in reduced psychological distress and rates of depression. A licensed mental health practitioner (therapist or nurse) and the individual actively worked together toward recovery based on a psychological assessment. Standardized measures of mood (28-item General Health Questionnaire/GHQ-28), cognitive state (mini-mental state examination), and function (Barthel ADL Index, Frenchay Activities Index) were taken at different times. Hill et al. reported that 6 months later, all psychological and activity measures favored problem-solving therapy. At 12 months, patients in the

problem-solving therapy group had significantly lower GHQ-28 scores and lower median Present State Examination symptom scores (Hill et al. 2019). In addition, the problem-solving therapy group was more satisfied with some aspects of care.

Astrocytes in Major Depressive Disorder (MDD) and PSMD

MDD is the most prevalent form of depression, often manifested with a long-lasting and recurrent psychiatric condition. It is reported that MDD affects 20% of the population throughout their lifetimes (Kessler and Bromet 2013), and it is now considered the leading cause of disability worldwide. The symptoms of MDD included depressed (low) mood; anhedonia; feelings of hopelessness (despair), worthlessness, or guilt; changes in appetite, weight, and sleep; an inability to feel pleasure (anhedonia); fatigue; and suicidal ideation. Studies suggest that the neural activities of specific brain circuits are altered in response to external stimuli, such as stress, as a result of maladaptive molecular and cellular changes in MDD. Astrocytes interact intimately with neurons to support and regulate essential functions and mediate information processing through tripartite synapses in the brain, where astrocyte processes wrap tightly around pre-synaptic and post-synaptic sites (Araque et al. 1999; Halassa et al. 2007; Haydon 2001; Volterra and Meldolesi 2005; Khakh and Sofroniew 2015). Therefore, astrocytes have been receiving increasing attention in mood disorders since significant abnormalities were observed in the postmortem brain of MDD patients. Indeed, studies using postmortem brain specimen and animal models of depression provide a large body of evidence that astrocytes play an important role in MDD and PSMD.

Astrocyte in MDD

Studies from Human Postmortem Brain Specimens

Brain imaging studies have revealed marked volume reductions in the hippocampus and medial prefrontal cortex (mPFC) in MDD (Drevets 2000; Sheline 2003). Studies from human specimens showed that abnormalities in glial cells may alter normal brain function and likely contribute to mood disorder development. Profound alterations of astrocytes connecting to mood disorders were observed from postmortem brain specimen. These include changes in cell number and cell morphology in patients who had mood disorders. Prominent reductions in glial cell number and packing density have been reported in independent laboratories based on studies using postmortem brains from subjects with mood disorders in different regions of the PFC, the anterior cingulate cortex (Gittins and Harrison 2011; Cotter et al. 2001a), and the amygdala (Rajkowska 2000; Altshuler et al. 2010; Ongur et al. 1998; Bowley et al. 2002). Such a striking cellular deficit in glial number suggests

that glia may be unique targets for novel strategies in the treatment of mood disorders.

Altered expression of astrocyte-specific biomarkers was also observed in postmortem brain specimens of individuals that had suffered from mood disorders, for example, low levels of GFAP have been found in the hippocampus, PFC, anterior cingulate, and amygdala (Webster et al. 2001; Gittins and Harrison 2011; Altshuler et al. 2010). In postmortem brains of suicide completers, reduced GFAP mRNA and protein in the mediodorsal thalamus and caudate nucleus were observed in depression-related suicides compared with controls, suicides not linked to depression (Torres-Platas et al. 2016). Furthermore, a regional comparison revealed that GFAP expression in both subcortical regions was, on average, between 11- and 15-fold greater than in the cerebellum and neocortex. Examining astrocyte morphology by immunohistochemistry showed that astrocytes in both thalamus and caudate displayed larger cell bodies and extended more ramified processes across larger domains than the previously described cortical astrocytes. This study reveals that astrocytic abnormalities are not brain wide and suggests that they are restricted to cortical and subcortical networks known to be affected in mood disorders.

S100B proteins are a family of acidic proteins that influence cellular responses along calcium signal transduction pathways primarily produced by astrocytes. It was found that S100B was elevated in the blood serum and cerebrospinal fluid of MDD patients, and antidepressant treatment could lower S100B levels in parallel with reduced depressive symptoms (Matthias et al. 2013; Schroeter et al. 2002). In addition, a systematic and quantitative meta-analysis demonstrated that both young and older subjects suffering from mood disorders showed elevated S100B values in blood serum compared to control subjects. Also, higher levels of S100B were found in older compared with younger adult subjects, indicating that glial pathology is modified by age in mood disorders (Schroeter et al. 2011). Thus, S100B can be considered as a new marker for MDD.

Changes to gene transcription and protein expressions relating to normal astrocyte function were also found in patients diagnosed with mood disorders. For example, gene and protein expression of some astrocytic function-related proteins, including glutamine synthetase, glutamate transporters, and even gap junction proteins, was downregulated in patients with depression (Sequeira et al. 2009; Bernard et al. 2011). Altered cortical glutamatergic and GABAergic signal transmission in depression is associated with downregulation of high-affinity glutamate transporters GLT1 and glutamine synthetase (Choudary et al. 2005). Using immunostaining, a reduction of blood vessel coverage by AQP4 astrocytic endfeet was reported in MDD subjects (Rajkowska et al. 2013).

Postmortem histopathologic studies of depressed patients strongly suggest that the abnormalities in astrocytic functions, such as regulation of water homeostasis, blood flow, glucose transport and metabolism, the blood-brain barrier, glutamate and GABA turnover, and synaptic plasticity, may contribute to the pathophysiology of MDD.

Studies from Animal Models

While studies using postmortem brain specimens provide insights into pathological changes of astrocytes in MDD, studies using animal models may provide the underlying molecular mechanisms by which astrocytes participate in disease etiology. Stressful life events including acute and chronic stress increase the risk for MDD in humans (Arsenault-Lapierre et al. 2004). Thus, in animal experimental studies on MDD, mice and rats are exposed to acute stress (e.g., tail suspension test, forced swim test, unavoidable foot shock test, social defeat test, or restraint stress) or chronic unpredictable stress (CUS) to induce depressive-like states (Henn and Vollmayr 2005).

Due to the nature of tripartite synapses, astrocyte-derived substances such as glutamate, D-serine, lactate, and ATP can actively modulate synaptic function. Meanwhile, the changes in the expression of astrocyte-specific glutamate transporters, such as GLT1 and GLAST1; glutamate receptors, such as mGluR5; enzymes, such as glutamate synthesis and lactate dehydrogenase; and ion channels and gap junctions may affect/regulate ion homeostasis, synaptic transmission, pH, redox state, etc. These multiscale and multimodal interactions of astrocytes with synaptic circuits are likely to contribute to behavior. Because neuronal synaptic changes are a hallmark of depression and astrocytes are integral to tripartite synapses, astrocytes are very likely to participate in the pathology of depression and anxiety disorders. Indeed, a large number of studies from rodent model have provided evidence of astrocytic involvement in MDD. For extensive reviews of astrocytes in this area, readers are advised to consult a few detailed reviews (Wang et al. 2017; Bender et al. 2016; Park and Lee 2020). Here, I will briefly summarize the recent progress in this area.

An attractive hypothesis for MDD is that impaired ATP release from astrocytes causes MDD (Illes et al. 2020; Cao et al. 2013). Cao et al. identified ATP as a key factor involved in astrocytic modulation of depressive-like behavior in the hippocampus and prefrontal cortex of adult mice with chronic social defeat stress (Cao et al. 2013). Low ATP abundance was observed in the brains of mice that were susceptible to chronic social defeat. Furthermore, they found that the administration of ATP induced a rapid antidepressant-like effect in these mice. Both a lack of inositol 1,4,5-trisphosphate receptor type 2 (IP_3R2) and transgenic blockage of vesicular gliotransmission-induced deficiencies in astrocytic ATP release caused depressive-like behaviors that could be rescued via the administration of ATP. Using transgenic mice that express a Gq G-protein-coupled receptor (GPCR) only in astrocytes to enable selective activation of astrocytic Ca^{2+} signaling, they also found that stimulating endogenous ATP release from astrocytes induced antidepressant-like effects in mouse models of depression. Moreover, P2X2 receptors in the medial prefrontal cortex mediated the antidepressant-like effects of ATP. Their results highlight astrocytic ATP release as a biological mechanism of MDD. However, the data above using IP_3R2-deficient mice is inconsistent with a study by Petravicz et al. (Petravicz et al. 2014), who found that the mice did not show any abnormalities in the open field test or the tail suspension test. Therefore, it remains difficult to clarify

the relationship between astrocytic Ca^{2+} signaling and depression, suggesting a complex nature of depression and the lack of decisive behavior tests to evaluate it.

The lateral habenula (LHb) is a nucleus that relays information from the limbic forebrain to multiple monoamine centers and has recently emerged as a key brain region in regulating negatively motivated behavior and the pathophysiology of major depression (Cui et al. 2018; Li et al. 2013b; Hu et al. 2020; Baker et al. 2016; Yang et al. 2018). In a rat depression model of congenitally learned helplessness, Cui et al. recently discovered that Kir4.1 in astrocytic membrane processes was upregulated in the lateral habenula (LHb) (Cui et al. 2018). Their study using electrophysiology and modeling data shows that the level of Kir4.1 in astrocytes tightly regulates the degree of membrane hyperpolarization and the amount of bursting activity of LHb neurons. Astrocyte-specific gain and loss of Kir4.1 in the LHb bidirectionally regulates neuronal bursting and depression-like symptoms. Together, their results show that a glia-neuron interaction at the perisomatic space of LHb is involved in setting the neuronal firing mode in models of a major psychiatric disease. Therefore, targeting Kir4.1 in the LHb might be a potential strategy for treating clinical depression.

Neuroinflammation contributes to the cognitive impairments accompanying many neurological disorders. Chronic stress and neuroinflammation are considered to be fundamental in the etiology of MDD. Astrocyte dysfunction and inflammation have been proven to be associated with the pathogenesis of MDD. Using mouse depression models of 6 weeks of chronic unpredictable mild stress (CUMS) or 10 days of lipopolysaccharide (LPS) intraperitoneal injection, Leng et al. explored intermediary components that are modulated by stress and neuroinflammation (Leng et al. 2018). They found that multiple endocrine neoplasia type 1 (Men1; protein: menin) expression is attenuated in the brain of mice exposed to CUMS or LPS. Astrocyte-specific deletion of Men1 (GcKO) led to depressive-like behaviors in mice and enhanced IL-1β production through NF-kB activation. Further, they observed that depressive-like behaviors in GcKO mice could be restored by an NF-kB inhibitor or an IL-1β receptor antagonist. Importantly, they identified a SNP in human MEN1, where G503D substitution is associated with a higher risk of MDD onset. G503D substitution abolished menin-p65 interactions, thereby enhancing NF-kB activation and IL-1β production. The study revealed a distinct role of tumor suppressor menin in astrocytes in regulating astrocytic inflammation in depression, and menin may be an attractive therapeutic target in MDD.

IL-10 is a key cytokine that is mainly produced by astrocytes and microglia and that represses excessive inflammatory responses. In the CNS, IL-10 is upregulated after various insults. Astrocytes isolated from transgenic mice deficient with IL-10 are prone to characteristic A1 reactive astrocytes and these transgenic mice exhibited increased immobility time in the forced swim test and defective learning and memory behavior in the Morris water maze test (Zhang et al. 2020a), suggesting IL-10 contributes to the depression-like behavior and memory deficits.

It was found that local application of TFNα at pathological levels activates astrocyte TNF receptor type 1 (TNFR1), which in turn triggers an astrocyte-neuron signaling cascade that results in persistent functional modification of hippocampal

excitatory synapses. Astrocytic TNFR1 signaling induced hippocampal synaptic alteration and contextual learning-memory impairment. This process may contribute to the pathogenesis of cognitive disturbances (Habbas et al. 2015). High extracellular levels of TNFα can trigger release of glutamate from astrocytes (Santello et al. 2011). Thus, the mechanism by which the cytokine TNFα affects cognitive disturbances upon CNS inflammation is via a local increase of TNFα in the hippocampal dentate gyrus that activates TNFR1, which then triggers an astrocyte-neuron signaling cascade resulting in a persisting modification of hippocampal excitatory synapses (Habbas et al. 2015). Astrocytes are not only key to normal cognitive functions, but also the modification of synapses following neuroinflammation.

Astrocytes provide metabolic support to neurons. One mechanism is through the astrocyte-neuron lactate shuttle (Pellerin and Magistretti 1994; Magistretti and Pellerin 1996; Belanger et al. 2011; Magistretti and Allaman 2015). It is reported that peripheral administration of lactate exerts antidepressant-like behavioral effects (Carrard et al. 2018). These behavioral effects of lactate may be brought about by its ability to increase synaptic excitability.

The glutamatergic predominance in the excitatory-inhibitory balance is postulated to be involved in the pathogenesis of depression. Such an imbalance may be induced by astrocyte ablation which reduces glutamate uptake and increases glutamate levels in the synaptic cleft, causing depression-like behaviors. A causal relation between astrocytic dysfunction and depression is also provided by animal studies. The selective destruction of frontocortical astrocytes with the gliotoxin L-α-aminoadipic acid (L-AA) is sufficient to trigger a depressive-like phenotype (Banasr and Duman 2008; Domin et al. 2014). Both the behavioral and GFAP level changes could be prevented by injection of 3-((2-methyl-4-thiazolyl)ethynyl)pyridine (MTEP), a mGluR5 antagonist, through the inhibition of glutamatergic transmission (Domin et al. 2014). The results demonstrate that glial ablation in the PFC is sufficient to induce depressive-like behaviors similar to chronic stress, supporting the hypothesis that loss of glia contributes to the core symptoms of depression. Astrocyte dysfunction therefore may lead to excitatory-inhibitory imbalances, resulting in mood disorders such as depression and anxiety. Astroglial degeneration in the prefrontal cortex is a useful rat depression model.

Gap junctional communication is a main determinant of astrocytic function. Rats exposed to CUS, a rodent model of depression, showed behavioral deficits in sucrose preference test (SPT) and novelty suppressed feeding test (NSFT) and exhibited significant decreases in diffusion of gap junction channel-permeable dye and expression of Cx43, a major component of astrocyte gap junctions, and abnormal gap junction ultrastructure in the PFC (Sun et al. 2012). The results showed that infusions of gap junction blocker carbenoxolone (CBX) induced anhedonia in SPT and anxiety in NSFT, a core symptom of depression. Gap junction dysfunction contributes to the pathophysiology of depression.

Water channel AQP4 is expressed in astrocytes in the brain and is also involved in the pathogenesis of depression. Using a mouse model of depression induced by repeated corticosterone injections (Zhao et al. 2008), AQP4 knockout mice exhibit exacerbated depression-like behaviors based on forced swimming test (FST) and

tail suspension test (TST) (Kong et al. 2014). These knockout mice also show a significant loss of astrocytes; aggravated downregulation of excitatory amino acid transporter 2 (EAAT2), synapsin-1, and glial cell line-derived neurotrophic factor (GDNF); and less hippocampal neurogenesis. Thus, astrocytic AQP4 can modulate astrocytic function and adult neurogenesis during the pathogenesis of depression and might be a potential target for the treatment for depression.

Blockade of astrocytic glutamate transporter GLT1 induces depressive-like behaviors in rats (Bechtholt-Gompf et al. 2010; John et al. 2012). Dysfunction or imbalance of the monoamine- or L-glutamate (L-Glu)-mediated synaptic transmission is known to be a pathogenic cause of many disorders. Astrocytes take up synaptic L-Glu during synaptic transmission through excitatory amino acid transporters GLT1 and GLAST. L-Glu is subsequently metabolized to L-glutamine (L-Gln) by glutamine synthetase (GS). Then, release of astrocytic L-Gln is used as a neuronal L-Glu precursor, making up the glutamine cycle. Expression levels of astrocyte transporters and metabolizing enzymes are dynamically regulated by synaptic activity, which empowers astrocytes to support synaptic transmission. Pharmacological blocking of astrocyte glutamate buffering by blocking GLT1 triggered depressive behaviors in the form of latency to drink sucrose solution, increased intracranial self-stimulation, or decreased social interaction (John et al. 2012). Decreased GLT1 and GLAST expression may cause impaired L-Glu turnover, which contributes to depression. Evidence that riluzole, which activates L-Glu transporters, reverses the decreased GFAP expression in rat prefrontal cortex and improves depressive-like behavior supports the involvement of impaired L-Glu turnover in depression pathogenesis (Banasr and Duman 2008). The role of astrocytes in the excitatory-inhibitory imbalance hypothesis of depression and anxiety is related to changes in glutamate receptor function.

Depression and anxiety are associated with NMDAR, and its antagonist ketamine was shown to produce a rapid antidepressive effect (Yang et al. 2018; Li et al. 2010). NMDARs are activated after binding of the agonist glutamate to the NR2 subunit along with a co-agonist, either L-glycine or D-serine, to the NR1 subunit at a glycine modulatory site to function as a gatekeeper. L-serine is synthesized by astrocytes, which is then transported to neurons for conversion to D-serine by serine racemase (SR). Substantial evidence suggests that D-serine is the most relevant co-agonist in forebrain regions, supporting its role in fear conditioning and anxiety disorders (Wolosker and Balu 2020). Transgenic mice overexpressing SR which increase the availability of astrocyte D-serine led to a reduced depressive phenotype based on the forced swim, novelty suppression of feeding and olfactory bulbectomy paradigms; chronic dietary D-serine supplement mimics the depression-related behavioral phenotype observed in SR transgenic mice (Otte et al. 2013). The acquisition and extinction of fear memory engages the SR/D-serine system in the mouse amygdala, and D-serine administration facilitates fear extinction (Balu et al. 2018).

Overall, the aforementioned studies indicate that astrocytes play a role in depression-like behaviors using different mechanisms, and impaired astrocytic function is necessary and sufficient to induce depression-like behaviors in animal experimental studies.

Astrocytes in PSMD

Although there were few functional studies on the role and mechanism depression in humans, studies from human specimens and animal models of MDD may provide insights into the mechanism and therapeutic strategies for PSMD. Generally, there are two causes of mood swings after stroke: biological changes and lifestyle changes. Biological changes are caused by damage in the emotion centers of the brain. Few studies have been done on the relationship between biological changes and PSMSD at cellular and molecular levels. Data from experimental studies using rodent models might provide insight on PSMDs, depression, and anxiety in general. Since MRI studies have found significant alterations in different brain regions in MDD patients, such as in the frontal lobe, hippocampus, temporal lobe, thalamus, striatum, and amygdala (Pandya et al. 2012; Zhang et al. 2018), whether stroke patients develop PSMD might be dependent on the region that is injured. On the other hand, ischemic stroke causes changes in morphology, metabolism, and gene expression in reactive astrocytes. Any changes related to glutamate synthesis, transportation, and degradation after stroke may affect mood swings.

The monoaminergic hypothesis of depression postulates symptoms to be a result of an imbalance in the central monoaminergic system including serotonergic, dopaminergic, and/or noradrenergic neurotransmission (Marathe et al. 2018). Astrocytes express transporters for norepinephrine and serotonin (Inazu et al. 2003; Hirst et al. 1998), which are the targets of several classical antidepressant drugs. This raises a possibility that antidepressants can have direct effects on astrocytes. These studies suggest that astrocytes may exert control of serotonergic and noradrenergic transmission and are thus cellular targets for antidepressant drugs that block the reuptake of monoamines by astrocytes.

Wang et al. developed rat model for post-stroke depression (PSD) using middle cerebral artery occlusion (MCAO), followed by an 18-day chronic mild stress (CMS), and assessed depression-like behavior and the effects of the antidepressant citalopram (Wang et al. 2008). Using the open-field test (OFT) and the sucrose consumption test, they found that citalopram could ameliorate the behavioral abnormalities, suggesting that the ischemic rat CMS model is an appropriate model for PSD.

Inflammation and alterations in glutamate neurotransmission are two novel pathways to pathophysiology in mood disorders (Haroon et al. 2017). Stroke causes dysfunction of glutamate transporters and reduced glutamate uptake by astrocyte in acute phase. Increasing data indicate that inflammation causes impaired astrocytic glutamate uptake, and patients with depression and anxiety have increased inflammation (Haroon et al. 2017). Since inflammation also occurs in ischemic stroke, inflammation-induced impairment of glutamate uptake may contribute to the development of or enhanced predisposition for PSMD. Elevated glucocorticoids due to illness-related stress could also downregulate glial activity and exacerbate or predispose patients to psychiatric illness via enhanced excitotoxicity (Cotter et al. 2001b). Since excitotoxicity is a common acute consequence of ischemic stroke, this may

contribute to the subsequent development of mood disorders such as post-stroke depression and anxiety.

Chen et al. showed that post-stroke enrichment environment (EE) increased high-mobility group box-1 (HMGB1) and interleukin-6 (IL-6) expression in astrocytes, led to decreased depression and anxiety-like behavior, and promoted angiogenesis and functional recovery compared to standard environment (Chen et al. 2017). EE mice treated with glycyrrhizin decreased, whereas EE mice treated with recombinant HMGB1 (rHMGB1) increased in the levels of IL-6 and p-AKT. Their study highlighted the role of the astrocytic HMGB1-IL6 pathway in PSMD in animal models.

Yu et al. found that GLT1 was downregulated in astrocytes in the post-stroke rat model (Yu et al. 2019b). Reduced expression of GLT1 in PSD astrocytes inhibited the formation of functional synapses by influencing glutamate metabolism. Another study from the same group investigated the effect of ceftriaxone, which increases GLT1 expression, on depression-like behaviors of rats after MCAO (Yu et al. 2019a). They found that treatment of ceftriaxone gradually increased GLT1 both in transcription and translation levels and inhibited depression-like behaviors by increasing locomotor and rearing activity and improving anhedonia of the rats. Moreover, ceftriaxone can promote glutamate circulation and synaptic plasticity by increasing astrocytic GLT1 levels. Their study indicates that reduction of GLT1 in astrocytes is one potential mechanism of pathogenesis of post-stroke depression.

Rats injected with the astrocyte-specific toxin L-AA in the mPFC, which is anatomically and functionally linked with cognitive and emotional processing, resulted in a pronounced loss of astrocytes in the region and adversely affected set-shifting, working memory, and reversal learning functions (Lima et al. 2014). The lesion sites also showed progressive neuronal loss and dendritic atrophy in surviving neurons, suggesting that L-AA-induced astrocytic loss in this brain region leads to neuronal damage that results in cognitive impairment. Therefore, it is clear that astrocytes play a key role in cognitive impairment, which also occurs after stroke.

The neurotrophic hypothesis in depression and anxiety disorders was proposed because lower serum levels of neurotrophic factors like brain-derived neurotrophic factor (BDNF) are often observed in patients with depression, while increased expression of BDNF and GDNF is observed in patients as a response to antidepressant treatment (Pisoni et al. 2018). BDNF overexpression in hippocampal astrocytes leads to antidepressant-like activity and increased neurogenesis in mice (Quesseveur et al. 2013). Recently, a study demonstrated that RAs expressed increased GDNF (Zhang et al. 2020b), and this suggests that RAs might play a role in improving PSMD through GDNF release.

D-Serine has also been found to play a role in post-traumatic stress disorder (PTSD) (Wolosker and Balu 2020). It was found that the single nucleotide polymorphism, rs4523957, in human serine racemase gene, is associated with PTSD based on postmortem human brain study (Balu et al. 2018). D-Serine might play a role in PSMD since stroke and traumatic injury have similar mechanisms of brain injury.

Overall, these data suggest that astrocytes/reactive astrocytes are an integral part of depression and anxiety through different mechanisms and may be a potential therapeutic target for PSMD.

Concluding Remarks

Ischemic stroke is a leading cause of human disability, but recovery of behavioral function in animal stroke models and young patients can be remarkable, much of which is due to neuroplasticity that involves the strengthening of existing synapses, synaptogenesis, or local sprouting. However, these effects are often accompanied by neurological problems because of failure to recruit larger and more diffuse networks to function normally. Beyond the disability in normal motor function, it is common that stroke survivors have depression and anxiety-like mood disorders. Although a large body of evidence indicates that astrocytes play a role in MDD from studies of both human postmortem specimen and animal models, there are fewer studies regarding the participation of astrocytes or reactive astrocytes in PSMD. Considering that astrocytes can influence neuronal function through a variety of mechanisms, future studies on the mechanisms by which astrocytes/reactive astrocytes play a role in PSMD should focus on the context of astrocyte-neuron interactions in stroke models.

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Astroglia and Obsessive Compulsive Disorder

Kohichi Tanaka

Introduction

Obsessive compulsive disorder (OCD) has a prevalence rate of 1–3% in the general population and has been ranked as one of the top ten leading causes of illness-related disability (American Psychiatric Association 2013; Kessler et al. 2005). OCD is characterized by persistent intrusive thoughts (obsessions) and repetitive behaviors (compulsions) (Leckman et al. 1997). There are various OCD-related disorders, including Tourette syndrome (TS), grooming disorders (e.g., skin-picking, trichotillomania), and autism spectrum disorders (ASD) that share considerable overlapping features with OCD (Browne et al. 2014). Although the neurobiological basis of OCD still remains obscure, neuroimaging studies in patients with OCD and OCD-related disorders have consistently identified hyperactivity in orbitofrontal cortex and striatum (Cerliani et al. 2015; Hou et al. 2014; Jung et al. 2017; Neuner et al. 2014). However, the cellular and synaptic abnormalities underlying this hyperactivity are unclear. The most prominent theory regarding the underlying mechanisms of OCD and OCD-related disorders is an increased excitation to inhibition (E/I) ratio due to increased glutamatergic excitation or reduced GABAergic inhibition (Albin and Mink 2006; Rubenstein and Merzenich 2003; Wu et al. 2012). A proper E/I ratio is achieved by factors expressed in neuron and glia. In astrocytes, both the glutamate transporter GLT1 and GABA transporter GAT-3 are critical for regulating the E/I balance (Aida et al. 2015; Aizawa et al. 2020; Boddum et al. 2016; Cui et al. 2014; Kersanté et al. 2013; Kiryk et al. 2008; Matos et al. 2018; Scimemi 2014; Sugimoto et al. 2018; Sugiyama et al. 2017; Tanaka et al. 1997; Zhao et al. 2018). Although astrocyte dysfunction has not been directly explored in OCD

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patients, several animal studies have found that astrocytes are involved in the pathophysiology of OCD. In this chapter, I highlight recent studies in which astrocyte dysfunction contributed to E/I imbalance, leading to pathological repetitive behaviors shared between patients with OCD, TS, and ASD.

Astrocytic Glutamate Transporter GLT1-Deficient Mice Exhibit Pathological Repetitive Behaviors

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system (CNS) and plays an important role in most aspects of normal brain function including cognition, learning, and memory (Nakanishi et al. 1998) Despite its importance as a neurotransmitter, excess glutamate is toxic to neurons, a phenomenon known as excitotoxicity (Choi 1994). Excitotoxicity is implicated in the pathophysiology of various neuropsychiatric diseases such as OCD, TS, and ASD (Albin and Mink 2006; Rubenstein and Merzenich 2003; Wu et al. 2012). Clearance of extracellular glutamate is critical for the maintenance of low extracellular glutamate concentrations and is achieved by the uptake of released glutamate by Na^+-dependent transporters (Tanaka 2000). There are five subtypes of Na^+-dependent glutamate transporters, GLAST (EAAT1), GLT1 (EAAT2), EAAC1 (EAAT3), EAAT4, and EAAT5. GLAST and GLT1 are predominantly expressed in glial cells, whereas EAAC1, EAAT4, and EAAT5 are expressed in neurons. GLT1 plays a critical role in the maintenance of extracellular glutamate homeostasis in the forebrain (Aida et al. 2015; Aizawa et al. 2020; Cui et al. 2014; Kiryk et al. 2008; Sugimoto et al. 2018; Tanaka et al. 1997). GLT1 null mice exhibited severe seizures and premature death (Tanaka et al. 1997). To overcome the premature lethality of GLT1 null mice, we generated astrocyte-specific GLT1-inducible knockdown (GLT1-KD) mice by crossing floxed-GLT1 mice ($GLT1^{flox/flox}$) (Cui et al. 2014), with mice expressing an inducible form of Cre under the astrocyte-specific, endogenous GLAST promoter ($GLAST^{CreERT2/+}$) (Mori et al. 2006). Tamoxifen was injected into $GLAST^{CreERT2/+}$; $GLT1^{flox/flox}$ mice from P19 for 5 days. In GLT1-KD mice, GLT1 protein levels were decreased by 60–80% in the cortex and striatum (Aida et al. 2015).

GLT1-KD mice show pathological repetitive behaviors including excessive self-grooming and tic-like head shakes. We investigated functional abnormalities of the whole brain network in GLT1-KD mice with functional magnetic resonance imaging (Abe et al. 2020). Blood oxygenation-level dependent-functional magnetic resonance imaging (BOLD-fMRI) is a tool for investigating whole brain functional connectivity and activity, based on the neurovascular coupling hypothesis (Drew 2019). A previous study showed that astrocytes could generate BOLD-fMRI responses without neuronal modulation (Takata et al. 2018). Indeed, GLT1 deletion affected the neurovascular coupling (Aizawa et al. 2020; Voutsinos-Porche et al. 2003). Thus, BOLD-fMRI may fail in GLT1-KD mice. In contrast, diffusion fMRI

(DfMRI) is an alternative functional imaging method to detect neural activity without interference from hemodynamics (Abe et al. 2017; Le Bihan et al. 2006; Tsurugizawa et al. 2013). We examined abnormalities of dynamic brain function in GLT1-KD mice by taking advantage of this DfMRI. Our DfMRI approaches analyzed three brain dynamic processes: resting state brain activity, functional connectivity (FC), and propagation of neural information. This approach revealed the hyperactive resting state activity and biased FC of the cortico-striatal-thalamic (CST) circuitry of GLT1-KD mice. In addition, we performed ignition-driven mean integration (IDMI) analysis, which examines how intrinsic local activation is propagated into whole brain regions (Deco and Kringelbach 2017; Deco et al. 2017). This analysis revealed that the phase-synchronized connectivity initiated from orbital area, primary motor area, and primary somatosensory area was increased in GLT1-KD mice, suggesting that GLT1-KD mice showed an unbalanced distribution of neural propagation in the CST circuitry. These global brain network functional abnormalities detected by DfMRI were associated with OCD-related behaviors in GLT1-KD mice.

Electrophysiological studies of basal corticostriatal synaptic transmission in GLT1-KD mice did not show any difference in the kinetics of either the AMPA or NMDA receptor-mediated excitatory postsynaptic currents (EPSCs), the AMPA/NMDA ratio, or paired-pulse ratio of evoked AMPA receptor-mediated EPSCs. However, a difference was observed in synaptic responses to a prolonged repetitive stimulation that triggers a massive glutamate release. In the control and GLT1-KD mice, the normalized EPSC amplitude decreased gradually during prolonged repetitive stimulation. Notably, this attenuation of EPSCs was significantly reduced in GLT1-KD mice (Aida et al. 2015). These data indicate that prolonged repetitive stimulation, but not a single episode of stimulation, leads to corticostriatal glutamatergic hyperactivity in GLT1-KD mice. The attenuation of EPSCs during repetitive stimulation is thought to reflect a presynaptic cycling process in which depleted docked vesicles are replenished by reserve pool vesicles (Hoshina et al. 2013). The presynaptic functions at corticostriatal synapses are intact in GLT1-KD mice because there is no difference in paired-pulse ratio between GLT1-KD and control mice. Therefore, the reduced attenuation of EPSCs in the striatum of GLT1-KD mice is likely induced by an increase in the extracellular glutamate concentration due to knockdown of the astrocytic glutamate transporter GLT1. Systemic administration of memantine, an NMDA receptor inhibitor, alleviated the pathological repetitive behaviors in GLT1-KD mice, whereas administration of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), had no effect on repetitive behaviors in GLT1-KD mice. These results suggest that astrocytic GLT1 has a critical role in controlling activity and FC across the CST circuitry via the modulation of the synaptic efficacy, and its dysfunction is involved in the pathophysiology of pathological repetitive behaviors (Fig. 1).

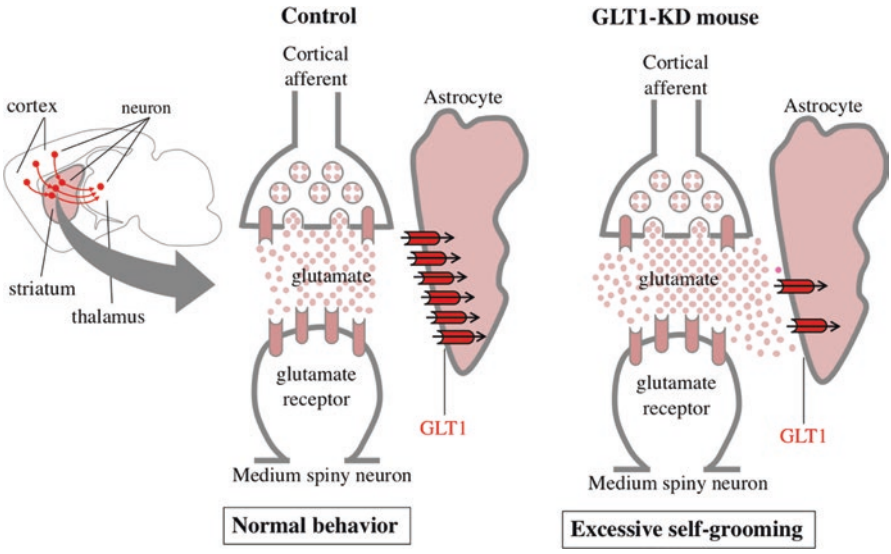

Fig. 1 GLT1-KD mice exhibit OCD-like behaviors via corticostriatal glutamatergic hyperactivity

GLT-1 Loss in *C. elegans* Drives Repetitive Behavior Through Presynaptic Activation of mGluR5

C. elegans is an excellent model system for studying how specific glia-neuron interactions control neuronal functions and animal behaviors because its nervous system is simple and extensively studied (Singhvi and Shaham 2019). Cephalic sheath (CEPsh) glia in *C. elegans* resemble vertebrate astrocytes in developmental, molecular, morphological, and functional properties. CEPsh glia express *ifa-4*, homologous to the glial fibrillary acidic protein (GFAP) and *glt-1*, homologous to the astrocytic glutamate transporter GLT1. GLT-1 loss, like postembryonic ablation of CEPsh glia, drives repetitive locomotor reversal behavior (Katz et al. 2019). These repetitive bouts of reversal locomotion are rescued by the loss of the vesicular glutamate transporter *eat-4*, suggesting that repetitive reversal behavior is dependent on presynaptic glutamate release. AVA is a major *C. elegans* interneuron regulating reversal behavior and RIM is a glutamatergic interneuron presynaptic to AVA. Thus, RIM-AVA synapses in *C. elegans* play a critical role in reversal behavior. CEPsh glia ensheath RIM-AVA synapses. GLT-1 mutants exhibit oscillatory glutamate release near postsynaptic sites of AVA and consequent oscillations in AVA activity. MGL-2, homologous to the metabotropic glutamate receptor 5 (mGluR5), is mainly expressed in RIM, and loss of MGL-2 suppresses the oscillation of AVA activity and repetitive reversal behavior in GLT-1 mutants. These data suggest that astrocytic GLT-1 loss allows glutamate to bind MGL-2 on presynaptic RIM, resulting in the induction of oscillatory glutamate release that leads to firing of the postsynaptic AVA and consequent repetitive reversal behavior (Fig. 2). In the mouse, GLT-1 loss

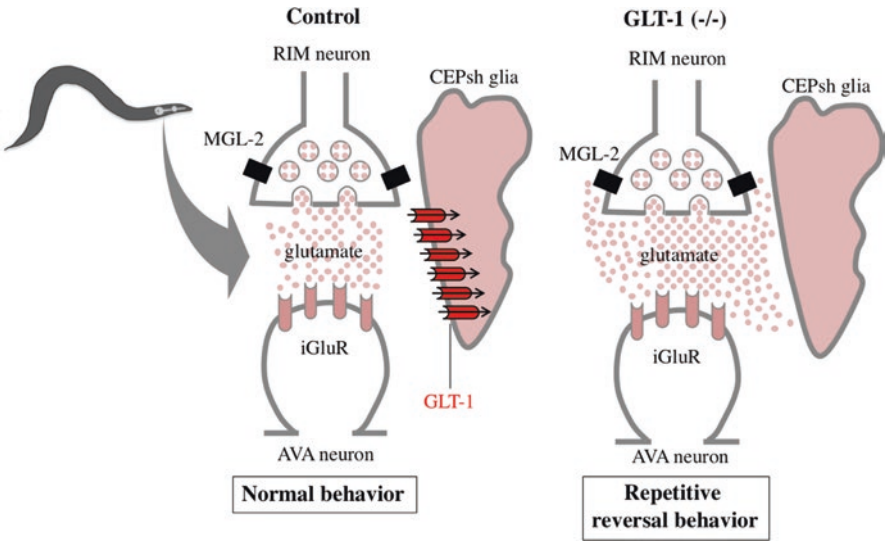

Fig. 2 GLT-1 knockout *C. elegans* exhibit repetitive behavior via presynaptic activation of MGL-2 CEPsh glia, cephalic sheath glia; iGluR, ionotropic glutamate receptor

induces repetitive behaviors (Aida et al. 2015). Thus, uncontrolled extracellular glutamate level due to astrocyte dysfunction is a driver of repetitive behaviors. In addition, excessive mGluR5 signaling is implicated in repetitive self-grooming behavior in mouse models for ASD and OCD (Ade et al. 2016; Silverman et al. 2010, 2012). That the same proteins act together in repetitive behaviors in *C. elegans* and mice suggests a common mechanism controlling repetitive behaviors.

Reduced Astrocyte Calcium Signaling Produces Abnormal Repetitive Behavior via Functional Upregulation of Astrocytic GABA Transporter GAT-3

Astrocytes display a form of excitability based on intracellular Ca^{2+} dynamics and have capabilities to regulate neuronal function (Bazargani and Attwell 2016; Shigetomi et al. 2016). In addition, recent studies suggest that astrocyte Ca^{2+} signaling is dysregulated in mouse models of neurological disorders (Khakh et al. 2017; Mustaly-Kalimi et al. 2018; Verkhratsky et al. 2017). The Khakh laboratory evaluated the consequences of reducing astrocyte calcium signaling in the adult mice (Yu et al. 2018). To reduce astrocyte Ca^{2+} signaling, they used a modified isoform of the human plasma membrane Ca^{2+} pump (hPMCA2w/b), which constitutively extrudes cytosolic Ca^{2+}. They delivered hPMCA2w/b to striatal astrocytes by injecting adeno-associated viruses with an astrocyte-specific GFAP promoter bilaterally into the dorsolateral striatum. hPMCA2w/b reduced the amplitude and shortened the

duration of astrocyte Ca^{2+} signals and reduced astrocyte basal Ca^{2+} levels. hPMCA2w/b-expressing mice exhibited excessive self-grooming, whereas they did not show any anxiety or depression-like phenotypes. Although reduction of striatal astrocyte Ca^{2+} signaling did not affect fast inhibitory or excitatory synaptic transmission onto medium spiny neurons (MSNs), MSN tonic inhibition was reduced in hPMCA2w/b-expressing mice. Astrocyte GABA transporter 3 (GAT-3) plays a critical role in tonic inhibition by regulating ambient GABA levels (Kersanté et al. 2013; Scimemi 2014). In hPMCA2w/b-expressing mice, GAT-3 protein levels were upregulated, and SNAP5114, a selective GAT-3 blocker, partially rescued self-grooming behavior. In vivo imaging in freely behaving mice revealed alterations of MSN activity, including increased correlated activity between MSNs during non-grooming episodes, an increase in the frequency of MSN activity during non-grooming episodes, and a reduction in the frequency of MSN activity during self-grooming, in hPMCA2w/b-expressing mice. However, it is not known how these alterations of MSN activity contribute to self-grooming, because there is no microcircuit level model of self-grooming. Furthermore, in a mouse model of Huntington's disease, astrocyte Ca^{2+} signaling was reduced and was associated with MSN tonic inhibition and excessive self-grooming, which was relieved by blocking GAT-3. These results indicate that upregulation of GAT-3 in striatal astrocytes contributes to excessive self-grooming via tonic GABA-mediated neuromodulation (Fig. 3).

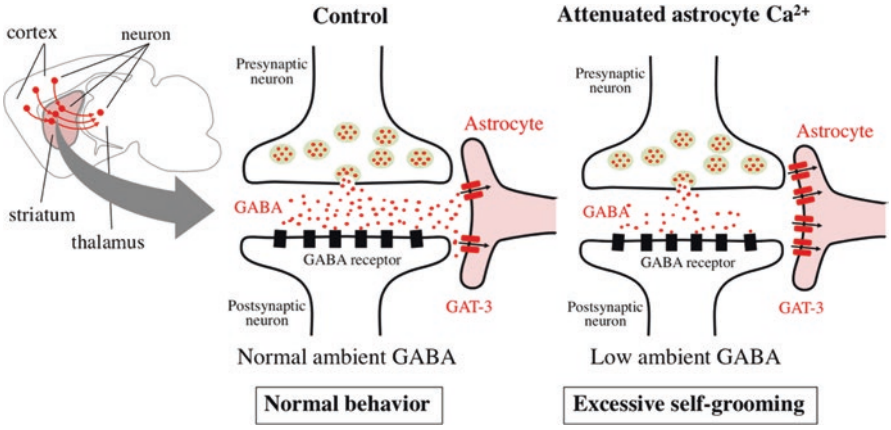

Fig. 3 Reduced astrocyte calcium signaling produces excessive self-grooming via functional upregulation of GAT-3

Conclusion

Neuroimaging studies in patients with OCD and OCD-related disorders have consistently identified hyperactivity in the corticostriatal network (Cerliani et al. 2015; Hou et al. 2014; Jung et al. 2017; Neuner et al. 2014). Studies on animal models of OCD and OCD-related disorders indicate that an increase in excitatory drive or a decrease in inhibitory drive in striatal microcircuitry may lead to enhanced MSN activity (Ahmari et al. 2013; Burguière et al. 2015). Because astrocytes play an important role in the modulation of neuronal excitability via the regulation of glutamate and GABA homeostasis, astrocytic dysfunction may play a critical role in the development of OCD. Although the roles of glutamatergic and GABAergic signaling in OCD have been investigated in patients, astrocytic alterations in patients have not received sufficient attention. Recent genetically engineered animals that exhibit excessive repetitive behaviors suggest that dysfunction of astrocytic GLT1 and GAT-3 plays a critical role in the development of pathological repetitive behaviors (Aida et al. 2015; Katz et al. 2019; Yu et al. 2018). Loss of astrocytic glutamate transporter GLT1 (GLT-1) results in high glutamate levels in the synaptic cleft causing aberrant excitatory transmission that contributes to excessive repetitive behaviors in mice and *C. elegans* (Aida et al. 2015; Katz et al. 2019). In addition, upregulation of astrocytic GABA transporter GAT-3 in the striatum results in loss of tonic inhibition via low ambient GABA levels in the synaptic cleft causing altered MSN activity that contributes to excessive self-grooming in mice (Yu et al. 2018). Although genome-wide association studies (GWAS) in patients with OCD reveal that significant associations were observed with neuronal genes encoding proteins involved in glutamatergic synaptic transmission, including DLGAP1 (disc large-association protein 1), PTPRD (protein tyrosine phosphatase delta), ISM1, and SLC1A1 (Arnold et al. 2006; Dickel et al. 2006; Mattheisen et al. 2015; Samuels et al. 2011; Stewart et al. 2013), no significant association was found in genes mainly expressed in astrocytes such as GLT1 and GAT-3. However, significant associations were observed with SLC1A2 (GLT1) in ASD, which accompanies repetitive behaviors (Autism Genome Project Consortium et al. 2007; Xu et al. 2008). Taken together, these studies suggest that astrocyte dysfunction may be involved in the pathophysiology of pathological repetitive behaviors in OCD and OCD-related disorders. Targeting glutamate or GABA uptake through astrocytes could lead to novel treatment options for patients with OCD and OCD-related disorders.

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Part III
Astroglia in Schizophrenia

Astrocytes in Neuropsychiatric Disorders: A Review of Postmortem Evidence

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Introduction

Glial cell types in the central nervous system (CNS) include microglia, oligodendrocytes, and, the most diverse type, astrocytes (Kettenmann and Ransom 2004). Astrocytes were named by Michael von Lenhossek at the end of the nineteenth century for the distinctive starlike shape of their complex arborization (Oberheim et al. 2012; Parpura and Verkhratsky 2012), and the term was later popularized by Santiago Ramon y Cajal (1913 and von Lenhossék (1895). Since the first astrocytes were observed, many different subtypes of astrocyte, displaying extensive morphological heterogeneity and different physiological properties, have been identified (Andriezen 1893). However, the primary function of this cell type is maintaining brain homeostasis (Andriezen 1893; Verkhratsky and Nedergaard 2018). An overview of different astrocyte subtypes is described in Table 1. Clinical and experimental evidence suggests critical roles for astrocytes in the pathogenesis of CNS disease. Studies examining astrocyte in postmortem brain tissues from patients diagnosed with neuropsychiatric disorders offer invaluable insight into the role of astrocytes in illnesses like schizophrenia (SCZ), major depressive disorder (MDD), and bipolar disorder (BPD) (Tarasov et al. 2019; Rajkowska and Stockmeier 2013; Peng et al. 2016).

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Table 1 Summary of astrocyte subtypes. FC, frontal cortex. "Mammals" indicates astrocyte subtype is found in humans, primates, and rodents

Class	Location	Species	Functions
Protoplasmic astrocytes	FC layers III and IV hippocampus	Mammals	Guide neuronal development (Hatten and Mason 1990)
			Regulate extracellular ions, metabolites, and neurotransmitters (Vernadakis 1996)
			Support neuronal and synaptic function (Araque et al. 1999)
Fibrous astrocytes	White matter	Mammals	Vascularization (Marin-Padilla 1995)
Interlaminar astrocytes	FC layers I and II	Primate, human	Long-distance coordination of intracortical communication (Oberheim et al. 2009)
			Coordinate blood flow (Oberheim et al. 2009)
Varicose astrocytes	FC layers V and VI	Higher-order primates, human	Long-distance coordination of intracortical communication (Sosunov et al. 2014)
			Vascularization (Sosunov et al. 2014)
Polarized astrocytes	FC layers V and VI	Higher-order primates, human	Long-distance coordination of intracortical communication (Verkhratsky et al. 2017)
Radial glia	Only in embryogenesis	Mammals	Embryonic neurogenesis Primary neural stem cells (Falk and Gotz 2017)
Bergmann glia	Cerebellum	Mammals	Regulate synapsis of Purkinje cells (Edwards et al. 1990)
Tanycytes	Hypothalamus	Mammals	Regulate neuroendocrine function (Prevot et al. 2018)
Müller glia	Retina	Mammals	Regulate synaptic activity in the inner retina Protect photoreceptors and neurons (Verkhratsky et al. 2019)
Radial glia-like neural stem cells	Neurogenic niches	Mammals	Local homeostasis Neurogenesis (Bonzano et al. 2018)
Velate astrocytes	Cerebellum	Mammals	Support enwrapped granule neurons (Verkhratsky et al. 2019) Isolate synaptic structures (Verkhratsky and Nedergaard 2018)
Perivascular and marginal astrocytes	Close to pia mater	Mammals	Form the pial and glia limitans barrier (Verkhratsky and Nedergaard 2018)
Pituicytes	Pituitary	Mammals	Release hormone Supply for synaptic neurotransmission in neurohypophysis (Garcia-Segura and McCarthy 2004)
Gomori-positive astrocytes	Hypothalamus and hippocampus	Mammals	Positive for Gomori's chrome staining Supply heme to neurons for the synthesis of heme enzymes Provide specific metabolic needs of neurons through high glucose metabolism (Verkhratsky and Nedergaard 2018)
Surface-associated astrocytes	Cortical surface	Mammals	Form the glia limitans (Feig and Haberly 2011)
Ependymocytes, choroid plexus cells, and retinal pigment epithelial cells	Ventricles and subretinal	Mammals	Produce cerebrospinal fluid (Verkhratsky and Nedergaard 2018)

Postmortem Changes in Astrocytes in Schizophrenia (SCZ)

A recently posited gliocentric hypothesis of schizophrenia suggests that suppression of glial progenitor cell differentiation during fetal development impacts astrocyte maturation, leading to reduced synapse coverage and disruption of glutamatergic homeostasis (Dietz et al. 2020). Reactive changes in astrocytes in SCZ are proposed to occur later in disease as secondary responses to other factors like neuroinflammation and drug treatment and may contribute to inconsistencies found in postmortem analyses of astrocytes in SCZ (Dietz et al. 2020). This idea is derived from neuroimaging, experimental data, and postmortem neuropathological studies. These studies show that astrocyte density, number, and morphology vary in SCZ in a manner that is highly brain region dependent (Williams et al. 2013; Benes et al. 1986, Bruton et al. 1990; Rajkowska et al. 2002a). In the middle frontal gyrus, hypertrophic astrocyte morphology is found in subjects with SCZ (Catts et al. 2014a), but in the subgenual cingulate white matter, a decrease in astrocyte density is reported in SCZ subjects compared to controls (Williams et al. 2014a). Astrocyte number was reportedly downregulated (Pakkenberg 1990) or upregulated (Barley et al. 2009) in the mediodorsal nucleus of the thalamus in SCZ in different studies. Astrocyte density varies across different subregions of the dorsolateral prefrontal cortex (DLPFC) (Rajkowska et al. 2002b), but there was no significant change in astrocyte number and density in hippocampal subfields of SCZ subjects compared to controls following stereological counting of morphologically identified (Nissl stain) cells (Schmitt et al. 2009). Yet, in the subiculum and CA1 in the hippocampus, there was a positive association between astrocyte number and disease duration in SCZ patients (Schmitt et al. 2009). A similar association between subiculum astrocyte number and age was also found in control subjects, suggesting age, rather than diagnosis, has a greater effect on astrocyte expression in this brain region. Additionally, immunoreactive counts of vimentin, a structural protein used as an astrocyte marker, were unaffected in the ventromedial temporal, frontal, and calcarine cortices in SCZ (Arnold et al. 1996a). Overall, reports of astrocyte morphology and density in SCZ studies vary between brain regions and methodological approaches applied.

In addition to astrocyte morphology and cell counts, protein and mRNA expression of astrocyte markers are also used to assess astrocytes in postmortem tissue. The immunoreactivity and total protein and mRNA expression of the intermediate filament protein glial fibrillary acidic protein (GFAP) were increased in the olfactory tubercle at the mesolimbic system and ventromedial temporal, frontal, and calcarine cortices (Toro et al. 2006a; Markova et al. 2000), but decreased in the anterior cingulate cortex (ACC) and white matter of the subgenual cingulate cortex (Williams et al. 2013; Steffek et al. 2008; Williams et al. 2014b) in SCZ subjects. Other studies showed no change in GFAP expression in the DLPFC, primary visual cortex, and hippocampus (Catts et al. 2014a; Steffek et al. 2008; Trépanier et al. 2016). SCZ patients presenting with dementia had higher numbers of GFAP-positive astrocytes, increased GFAP mRNA and protein expression, enlargement of astrocyte soma, and thickening of astrocytic processes compared to SCZ patients without dementia

(Arnold et al. 1996b). Therefore, it appears that age and dementia are two essential factors associated with higher astrocyte number. Overall, GFAP expression is altered in SCZ subjects compared with controls depending on the brain area studied. A summary of GFAP expression changes in SCZ is shown in Table 2.

Other commonly used astrocyte markers include vimentin, excitatory amino acid transporter (EAAT1/2), aldolase C, and S100 calcium-binding protein B (S100B) (Hwang et al. 2013; Feresten et al. 2013a; Katsel et al. 2011a, b). The protein expression of aldolase C was upregulated (Johnston-Wilson et al. 2000a; Martins-de-Souza 2010) or downregulated (Prabakaran et al. 2004; English et al. 2009) in SCZ depending on the brain region studied. Conversely, vimentin protein expression was unchanged in studies of the prefrontal cortex (Feresten et al. 2013a) and ventromedial temporal, frontal, and calcarine cortices (Arnold et al. 1996a). Interestingly, S100B mRNA expression was unchanged in the superficial layers or the underlying white matter of the cingulate cortex in SCZ subjects; however, it was significantly reduced in the deep layers of the anterior cingulate gyrus (Katsel et al. 2011b), suggesting lamina-specific changes in astrocyte expression (Arnold et al. 1996a; Feresten et al. 2013a). S100B immunopositive cells were increased in several brain regions such as ACC, DLPFC, orbitofrontal cortex, mediodorsal nucleus of the thalamus, and pyramidal layer of the hippocampus in a subset of SCZ subjects (Steiner et al. 2008). White matter levels of S100B were significantly increased in paranoid SCZ relative to residual SCZ subjects; however, this effect was driven by oligodendrocyte rather than astrocyte labeled S100B immunopositive cells (Steiner et al. 2008). In the absence of co-labeling with additional astrocyte markers, S100B labeled cell counts should be interpreted cautiously (Steiner et al. 2007).

EAAT2 mRNA and protein, commonly used markers of astrocytes, were increased in the prefrontal cortex Brodmann areas (BA) 9 and 10 in subjects with SCZ (Matute et al. 2005). However, significant reductions in mRNA (Ohnuma et al. 1998), significant increases in mRNA (Shao and Vawter 2008), and no change in mRNA or protein in the DLPFC and ACC (Bauer et al. 2008) have also been reported in SCZ. EAAT1 mRNA was increased in the ACC but unchanged in the DLPFC (Bauer et al. 2008), while EAAT1 protein was decreased in the DLPFC but unchanged in the ACC in SCZ (Bauer et al. 2008; Shan et al. 2013). Posttranslational modification of EAAT2 by glycosylation, necessary for EAAT2 localization to the membrane, is reduced in the DLPFC but unchanged in the ACC in SCZ (Bauer et al. 2010). In other brain regions, such as the hippocampus and superior temporal gyrus, an overall downregulation in EAAT2 protein expression was found in SCZ (Shan et al. 2013). EAAT1 protein was also downregulated in the superior temporal gyrus but unchanged in the hippocampus (Bauer et al. 2008; Shan et al. 2013). Immunoblotting showed a significant reduction in EAAT2 protein expression in the mediodorsal and ventral tier nuclei in the thalamus in SCZ. Protein expression of EAAT1 was reduced in the mediodorsal nucleus in SCZ subjects, confirming findings of reduced EAAT1 mRNA expression in an enriched population of astrocytes cut from that brain region in the same study (McCullumsmith et al. 2016). Overall, EAAT1/2 expression is broadly unchanged or reduced in SCZ although expression varies based on the brain region and whether mRNA or protein is being measured

Table 2 GFAP expression in postmortem brain tissues of subjects diagnosed with schizophrenia (SCZ)

Study	Brain region	SCZ	Method
Pantazopoulos et al. (2010)	Amygdala, entorhinal cortex	NS (n = 11)	IHC, ICC
Damadzic et al. (2001)	Entorhinal cortex	NS (n = 21)	IHC
Dean et al. (2006)	BA9, 10, 46, 40	NS (n = 20)	WB, qPCR
Webster et al. (2001)	DLPFC and hippocampus	Astrocytes containing pGFAP in DLPFC ↓; NS in hippocampus (n = 15 per group)	IHC
Altshuler et al. (2010)	Amygdala	NS (n = 9)	IHC
Feresten et al. (2013b)	DLPFC (BA9)	GFAP protein↑ (n = 35)	WB
Toro et al. (2006b)	DLPFC (BA9, 32, 46) and OFC (BA11,12,47,45)	GFAP protein DLPFC ↑; GFAP protein OFC ↓ (n = 15)	IHC
Fatemi et al. (2004)	Lateral cerebellum	GFAP protein↓ (n = 15 per group)	WB
Hercher et al. (2014)	White matter adjacent to DLPFC (BA9)	GFAP area fraction↓ (n = 20)	IHC
Johnston-Wilson et al. (2000b)	BA 10	GFAP311 protein↓ (n = 24)	2-DE
Markova et al. (2000)	Olfactory tubercle at the mesolimbic system	GFAP ↑ immunoreactive astrocytes (n = 12)	3-D Golgi, IHC
Arnold et al. (1996a)	Ventromedial temporal, frontal, and calcarine cortices	GFAP immunoreactivity↑ in SZ patients with dementia (n = 21)	ICC
Steffek et al. (2008)	DLPFC, primary visual cortex, superior Temporal gyrus, ACC, and hippocampus	GFAP protein ↓ ACC (n = 23)	WB
Williams et al. (2014a)	Subgenual cingulate cortex (white matter)	GFAP immunoreactivity ↓ (n = 11)	ICC
Williams et al. (2013)	ACC	GFAP mRNA↓ (n = 11)	IHC
Catts et al. (2014a)	Middle frontal gyrus anterior to the premotor cortex (BA46)	NS (n = 37)	WB, qPCR
Steffek et al. (2008)	DLPFC, ACC, primary visual cortex, superior Temporal gyrus, and hippocampus	NS (n = 23)	WB

BA Brodmann area, *DLPFC* dorsolateral prefrontal cortex, *OFC* orbitofrontal cortex, *ACC* anterior cingulate cortex, *WB* western blotting, *ICC* immunocytochemistry, *IHC* immunohistochemistry, *NS* no significant change, *2-DE* two-dimensional gel electrophoresis.

(Hu et al. 2015). However, EAAT2 mRNA is also expressed in neurons, albeit at low levels. Neuronal EAAT2 gene expression is increased in SCZ and other neuropsychiatric and neurological disorders (O'Donovan et al. 2017), which should be taken into account when interpreting reports of EAAT2 mRNA expression changes in SCZ.

The use of different methods such as immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), and western immunoblot analysis to detect astrocyte marker protein expression may contribute to inconsistencies in reported changes in astrocyte marker expression in SCZ (Catts et al. 2014a; Davalieva et al. 2016). Differences in genetic risk, subject age, and cause of death of individuals with SCZ may also be factors (Barley et al. 2009; Gosselin et al. 2009). Increased immune activation, as indicated by increased expression of immune-related genes in postmortem brain transcriptomic studies, may underlie the hypertrophic astrocyte morphology and increase in GFAP expression in a subset of SCZ subjects (Catts et al. 2014a; Fillman et al. 2013, 2014; Catts et al. 2014b).

Postmortem Changes in Astrocytes in Major Depressive Disorder (MDD)

Postmortem studies have revealed significantly reduced glial cell counts and reduced cell density in subjects with MDD. There was a marked reduction in astrocyte counts in the amygdala, layers II, III, and V of the DLPFC and layer VI of the ACC (Bowley et al. 2002; Ongur et al. 1998; Rajkowska et al. 1999; Cotter et al. 2001a, 2002). In a small study ($n = 6$ MDD subjects), there was a 29% reduction in astrocyte density in the amygdala and a 36% reduction in the glia to neuron ratio. The changes in the amygdala were primarily in the left hemisphere (~53%). However, after the effects of age and sex were taken into account, the differences in glia to neuron ratio and astrocyte density were not significant in MDD subjects (Bowley et al. 2002). Studies examining astrocytes in the prefrontal cortex of MDD subjects found reduced cell counts in the prefrontal subgenual region (~24%) and reduced cell density (20–30%) in layers II/III of the DLPFC (Ongur et al. 1998; Rajkowska et al. 1999; Cotter et al. 2002). Overall, decreased astrocyte cell count and density are found in diverse brain regions in postmortem MDD studies.

In MDD patients who died by suicide, protoplasmic (gray matter) and fibrous (white matter) astrocytes were reconstructed for morphometric analysis. The Golgi staining method revealed that astrocyte cell bodies in layer VI of the ACC were spherical with varicose thorny processes projecting in every direction. Fibrous astrocytes of the white matter in the same subjects presented oblong cell bodies with long, unramified varicose processes extending in opposite directions. These differences between white and gray cortical matter astrocyte activation may indicate local inflammation of the white matter leading to changes in fibrous astrocytes (Torres-Platas et al. 2011). The hypertrophy observed in the white matter astrocytes is in

line with the neuroinflammation hypothesis of MDD (Maes et al. 2009). Reduced astrocyte count and density was identified in both the gray and white matter in different brain regions in non-suicide MDD subjects, while hypertrophy of astrocytes was observed only in the white matter of the ACC (Torres-Platas et al. 2011; Qi et al. 2019). Based on the relatively small number of postmortem studies conducted to date, we can posit that cortical and subcortical brain regions in MDD subjects consistently present reduced astrocyte count and density. While the hypertrophy of astrocytes reported in the ACC of MDD subjects may be attributed to local inflammation due to proinflammatory cytokines, differences in cell count and density are region-specific, and further studies are necessary to understand the role of these astrocyte changes. In summary, based on observations of altered astrocyte numbers from postmortem MDD histopathologic studies, it has been posited that abnormal astrocyte function may contribute to the pathophysiology of mood disorders (Cotter et al. 2001b; Rajkowska and Miguel-Hidalgo 2007; Hercher et al. 2009).

Protein expression of marker GFAP was reported to have decreased tenfold in the prefrontal cortex (BA 9, layers I–VI) in MDD subjects under 60 years of age. There was a positive correlation between age and GFAP expression in these subjects (Si et al. 2004). Immunoreactive astrocytes had decreased GFAP expression in the amygdala, cerebellum, thalamus, and caudate nucleus of subjects with MDD illustrating widespread astrocyte pathology in MDD (Zhao et al. 2016; Choudary et al. 2005; Altshuler et al. 2010; Fatemi et al. 2004; Qi et al. 2019; Torres-Platas et al. 2016). A summary of GFAP expression changes in MDD is shown in Table 3. EAAT1 protein expression and EAAT1 and EAAT2 immunoreactivity were decreased in the orbitofrontal cortex of MDD and MDD + alcohol-dependent subjects compared to controls (Miguel-Hidalgo et al. 2010). Other postmortem MDD studies have found decreased EAAT1 and EAAT2 mRNA and protein in the hippocampus, DLPFC, orbitofrontal cortex, locus coeruleus, and cortex (Medina et al. 2016; Zhao et al. 2016; Choudary et al. 2005; Miguel-Hidalgo et al. 2010; Chandley et al. 2014). No changes in the astrocyte-specific enzyme glutamine synthetase, which converts glutamate to glutamine, were found in any groups (Miguel-Hidalgo et al. 2010).

Connexin 43 and connexin 30 are gap junction membrane proteins that are essential for astrocyte communication. Protein expression of the predominant gap junction protein, connexin 43, was decreased in the orbitofrontal cortex in MDD subjects, in MDD + alcohol-dependent subjects, and in subjects diagnosed with alcohol dependence only. The average packing density of connexin 43 in the orbitofrontal cortex was decreased in alcohol-dependent subjects, while the area fraction of connexin 43 immunoreactivity and connexin 43 puncta packing density in the gray matter was significantly decreased in MDD and MDD + alcohol-dependent groups. Subject age positively correlated with connexin 43 puncta in MDD and control groups suggesting that connexin 43 expression and localization to gap junctions may be differentially effected by age (Miguel-Hidalgo et al. 2014). Connexin 30 puncta density was unchanged in the ACC of MDD subjects, including in MDD subjects with and without a history of child abuse who died by suicide. However, connexin 30 coupling to oligodendrocyte- and myelin-specific connexins

Table 3 GFAP expression in postmortem brain tissues of subjects diagnosed with major depressive disorder (MDD)

Study	Brain region	MDD	Method
Damadzic et al. (2001)	Entorhinal cortex	NS (n = 13)	IHC
Webster et al. (2001)	DLPFC and hippocampus	Astrocytes containing pGFAP in DLPFC ↓; NS in hippocampus (n = 15 per group)	IHC
Altshuler et al. (2010)	Amygdala	GFAP immunoreactive astrocyte density↓ (n = 11)	IHC
Toro et al. (2006b)	DLPFC (BA9, 32, 46) and OFC (BA11,12,47,45)	NS (n = 15)	IHC
Fatemi et al. (2004)	Lateral cerebellum	GFAP protein↓ (n = 15 per group)	WB
Muller et al. (2001)	Hippocampus	GFAP immunoreactivity↓ (n = 15)	ICC
Johnston-Wilson et al. (2000b)	BA 10	GFAP 76,119,311 protein↓ (n = 19)	2-DE
Qi et al. (2019)	DLPFC, ACC	NS (n = 5)	IHC, qPCR
Si et al. (2004)	Prefrontal cortex (gray matter, layers I-VI)	GFAP protein ↓ (n = 15)	WB

BA Brodmann area, *DLPFC* dorsolateral prefrontal cortex, *OFC* orbitofrontal cortex, *ACC* anterior cingulate cortex, *WB* western blotting, *ICC* immunocytochemistry, *IHC* immunohistochemistry, *NS* no significant change, *2-DE* two-dimensional gel electrophoresis.

(astrocyte-oligodendrocyte gap junctions) may be decreased in the ACC (Tanti et al. 2019). No correlation was found between connexin 30 coupling and age, postmortem interval, substance abuse, or antidepressant medications, suggesting a disease-related effect.

Postmortem Changes in Astrocytes in Bipolar Disorder (BPD)

BPD is characterized by elevated mood (mania or hypomania) with intervening periods of normal mood (euthymia) and recurrent episodes of depression (Strakowski et al. 2012). There is growing evidence that abnormalities in astrocytes, including altered cell density, morphology, and function, may contribute to the onset of BPD. As with other neuropsychiatric disorders, there is a paucity of effective treatments for BPD. Lithium is a first-line treatment and most effective in relapsed BPD, but it has many side effects and potential toxicity including renal failure (Close et al. 2014) and puerperal relapse (Wesseloo et al. 2016). Quetiapine, olanzapine, risperidone, ziprasidone, valproic acid, carbamazepine, and lamotrigine are considered second-line treatments (Miura et al. 2014); however, they show varying efficacy and tolerability (Vieta et al. 2010; Sidor and Macqueen 2011). In comparison to MDD,

antidepressants have little or no efficacy for depressive episodes associated with BPD and are used only as an adjunct to mood stabilizers for bipolar depression (Hirschfeld 2014). Lithium and mood stabilizers also have limited efficacy in treating bipolar depression, the leading cause of morbidity in patients with BPD (Baldessarini et al. 2010). Little is known about the role of astrocytes in bipolar depression. Further investigations of astrocytes may offer a novel therapeutic substrate for the treatment of BPD.

Histology studies in postmortem human prefrontal cortex, DLPFC, orbitofrontal cortex, frontal cortex, amygdala, ACC, entorhinal cortex, and hippocampus tissues have identified altered astrocyte cell numbers, morphology, and density in brain regions implicated in BPD (Strakowski et al. 2012). A study using computer-assisted three-dimensional morphometric cell counting found reduced density of glial cells in the DLPFC of subjects diagnosed with BPD, coupled with enlargement and changes in shape of glial nuclei across multiple lamina, although the type of glial cells was not specified (Rajkowska et al. 2001).

Other studies have measured the expression of astrocyte marker GFAP to elucidate changes in astrocyte number and morphology in the brains of individuals with BPD. Increased GFAP protein levels were found in the DLPFC of BPD subjects compared to controls (Feresten et al. 2013b). In contrast, no change in the density of GFAP immunoreactive astrocytes was reported in the amygdala of a similar BPD cohort (Altshuler et al. 2010). Others have reported no change (Pantazopoulos et al. 2010; Damadzic et al. 2001; Dean et al. 2006; Webster et al. 2001), reduced expression (Toro et al. 2006b; Fatemi et al. 2004; Hercher et al. 2014; Johnston-Wilson et al. 2000b; Muller et al. 2001), or increased expression (Feresten et al. 2013b; Qi et al. 2019; Rao et al. 2010) of GFAP protein levels in the amygdala, entorhinal cortex, ACC, DLPFC, hippocampus, cerebellum, frontal cortex, and orbitofrontal cortex in BPD subjects using immunochemistry or immunoblotting approaches. Even within the same brain region, for example, the DLPFC, GFAP protein levels were increased or unchanged in different studies (Dean et al. 2006; Feresten et al. 2013b). In addition to GFAP, phosphorylated GFAP is also used as an astrocyte marker. In a large-scale proteomic study of frontal cortex tissue, four GFAP isoforms, related to four potential sites for phosphorylation of GFAP, were differentially expressed in subjects diagnosed with a psychiatric disorder compared to unaffected controls. The GFAP500 phosphorylated form of GFAP was decreased in BPD subjects (Johnston-Wilson et al. 2000b). Overall, investigations of astrocyte density changes using GFAP as an astrocyte marker in BPD have yielded inconsistent results. In addition to discrepancies in reports of GFAP expression, constitutively expressed GFAP levels vary dramatically between cells with different activation states, that is, increased GFAP levels may imply that astrocytes are activated in a specific brain region rather than an increase in cell number (Feresten et al. 2013b; Qi et al. 2019). A summary of GFAP expression changes in BPD is shown in Table 4.

EAAT2 mRNA was significantly upregulated in the DLPFC of subjects with BPD compared to controls (Shao and Vawter 2008). In contrast, others reported no significant change in EAAT2 or EAAT1 mRNA in the DLPFC (Zhao et al. 2016; Choudary et al. 2005; Medina et al. 2013), ACC (Choudary et al. 2005), striatum

Table 4 GFAP expression in postmortem brain tissues of subjects diagnosed with bipolar disorder (BPD)

Study	Brain region	BPD	Method
Pantazopoulos et al. (2010)	Amygdala, entorhinal cortex	NS (n = 11)	IHC, ICC
Damadzic et al. (2001)	Entorhinal cortex	NS (n = 14)	IHC
Dean et al. (2006)	BA9, 10, 46, 40	NS (n = 8)	WB, qPCR
Webster et al. (2001)	DLPFC and hippocampus	NS (n = 15)	IHC
Altshuler et al. (2010)	Amygdala	NS (n = 10)	IHC
Rao et al. (2010)	Frontal cortex	GFAP protein and mRNA↑ (n = 10)	WB, qPCR
Feresten et al. (2013b)	DLPFC (BA9)	GFAP protein↑ (n = 34)	WB
Toro et al. (2006b)	DLPFC (BA9, 32, 46) and OFC (BA11,12,47,45)	GFAP protein OFC ↓ (n = 15)	IHC
Fatemi et al. (2004)	Lateral cerebellum	GFAP protein↓ (n = 15 per group)	WB
Muller et al. (2001)	Hippocampus	GFAP immunoreactivity↓ (n = 15)	ICC
Hercher et al. (2014)	White matter adjacent to DLPFC (BA9)	GFAP area fraction↓ (n = 20)	IHC
Johnston-Wilson et al. (2000b)	BA 10	GFAP500 protein↓ (n = 23)	2-DE
Qi et al. (2019)	DLPFC, ACC	GFAP mRNA↑; GFAP immunoreactive astrocytes↓ (DLPFC, n = 9; ACC, n = 7)	IHC, qPCR

BA Brodmann area, *DLPFC* dorsolateral prefrontal cortex, *OFC* orbitofrontal cortex, *ACC* anterior cingulate cortex, *WB* western blotting, *ICC* immunocytochemistry, *IHC* immunohistochemistry, *NS* no significant change, *2-DE* two-dimensional gel electrophoresis.

(McCullumsmith and Meador-Woodruff 2002), hippocampus (Medina et al. 2013), or locus coeruleus (Bernard et al. 2011). In general, EAAT1 and EAAT2 mRNA expression was not altered in BPD. However, little is known about the protein expression of these astrocyte markers. Postmortem studies of BPD typically have small numbers of subjects or are conducted by pooling BPD and MDD subjects, limiting interpretation of some findings (Zhao et al. 2016).

Subjects with BPD have altered levels of other proteins related to astrocyte function. Neuropathological analysis found a bilateral decrease in the density of S100B immunopositive astrocytes in hippocampal CA1 pyramidal layers of subjects with BPD (Gos et al. 2013). Protein and mRNA levels of S100B were decreased in BA 9 of the DLPFC but increased in BA 40 of the parietal cortex in subjects with BPD (Dean et al. 2006). Interestingly, a meta-analysis (n = 104 patients) showed higher levels of serum S100B in patients with BPD (da Rosa et al. 2016).

Glial cell-derived neurotrophic factor (GDNF) is a neurotrophic factor that is typically produced by reactive astrocytes upon brain injury and provides important neuroprotection to dopaminergic neurons (Cunningham and Su 2002). Some studies have reported lower serum GDNF in patients with manic and/or depressive stages of BPD (Takebayashi et al. 2006; Zhang et al. 2010). An increase in serum GDNF was observed after 8 weeks of treatment with mood-stabilizing drugs (Zhang et al. 2010). Plasma GDNF levels were also higher in the euthymic stage of disease compared to the manic stage in BPD patients or in healthy controls, suggesting GDNF is associated with different mood states in BPD (Barbosa et al. 2011). However, no significant change in serum GDNF levels was also reported by several studies (Otsuki et al. 2008; Tunca et al. 2014; Rybakowski et al. 2013). Again, findings related to peripheral GDNF are inconsistent. Many of these studies did not account for confounding factors like patient renal function, which significantly impacts serum protein levels (Onodera et al. 1999). In addition, the source of circulating neurotrophic factors in serum is not limited to astrocytes. It is also unknown whether peripheral GDNF levels correlate with GDNF levels in the brain. Studies have shown that GDNF penetrates the blood-brain barrier very poorly (Kastin et al. 2003).

Overall, the findings of astrocyte-related changes in BPD are heterogeneous. This may reflect differences in the diverse brain regions studied, the effects of chronic mood-stabilizing medication treatment, as well as the clinical heterogeneity of this disorder.

Factors That Affect Astrocytes in Postmortem Studies of Neuropsychiatric Disorders

GFAP is the most commonly used marker of astrocytes in human CNS (Nichols et al. 1993). Many of the postmortem studies that assess astrocyte changes in neuropsychiatric disorders utilize GFAP as a marker; however, it is worth noting that not all astrocytes express GFAP (Liddelow and Barres 2017), and overreliance on a single or small number of markers may limit detection of changes in the heterogeneous astrocyte subtypes in the human brain in disease. In Fig. 1, we show the relative gene expression ($\log_{10}$ FPKM) of GFAP and other astrocyte markers in different cell types collected from human brain and reported in the Brain-RNAseq database (Zhang et al. 2016). Data from Brain-RNAseq suggests that some commonly used markers are not exclusively, or even predominantly, expressed in astrocytes at the mRNA level. This is in agreement with work suggesting that classical astrocyte markers like excitatory amino acid transporter (EAAT2) are also expressed in neurons and that expression is increased in SCZ (O'Donovan et al. 2015; McCullumsmith et al. 2015) and decreased in MDD (Medina et al. 2016; Zhao et al. 2016; Choudary et al. 2005; McCullumsmith and Meador-Woodruff 2002), supporting the importance of using validated markers to assay astrocytes in the brain.

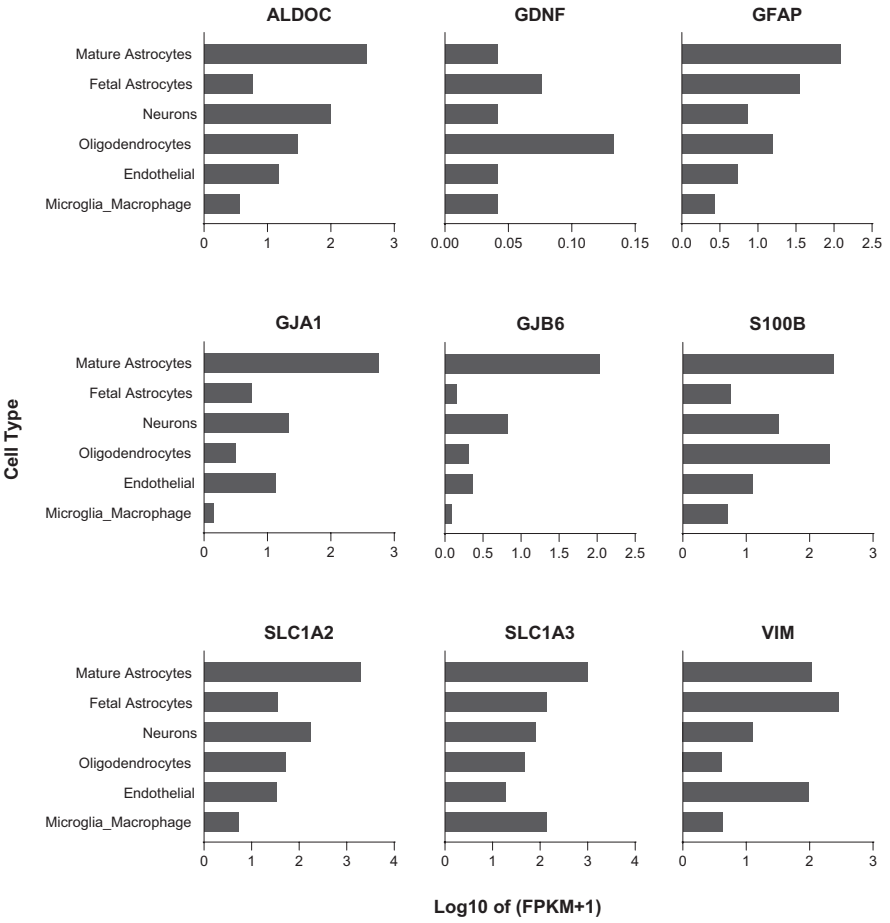

Fig. 1 Relative abundance and use of different astrocyte markers in human brain (Brain RNAseq) retrieved from Kaleidoscope. mRNA expression (Log10 of (FPKM+1)) for common astrocyte markers in six different cell types, fetal astrocytes, mature astrocytes, neurons, endothelial cells, microglia, and oligodendrocytes, was presented. These plots show that several commonly used astrocyte markers are also detected in other cell types at the mRNA level. ALDOC, aldolase C; GDNF, glial-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; GJA1, connexin 43; GJB6, connexin 30; S100B, S100 calcium-binding protein B SLC1A3, excitatory amino acid transporter 1 (EAAT1); SLC1A2, excitatory amino acid transporter 2 (EAAT2); VIM, vimentin

Postmortem studies offer invaluable insight into astrocyte expression in complex neuropsychiatric disorders like SCZ, MDD, and BPD. However, several factors must be considered when interpreting data obtained from postmortem studies, and they may contribute to inconsistent reports of astrocyte expression changes in the brain in severe mental illness. The length of time until tissue is stored (postmortem interval), the different methodologies applied to assay protein and gene expression, the heterogeneity of astrocyte cell types in different brain regions and lamina assayed, subject age and duration of illness, and differences in disease stage may

contribute to the lack of agreement in astrocyte expression changes reported in different neuropsychiatric disorders. In addition, postmortem studies often have limited sample sizes and cannot always account for additional variables including the effects of suicide or history of substance abuse on astrocyte expression in the brains of patients diagnosed with these disorders. Another important factor to consider is the use of medication; antipsychotics, antidepressants, and mood-stabilizing medications can significantly affect astrocyte expression (Peng et al. 2016; Trépanier et al. 2016; Fatemi et al. 2004; Tarasov et al. 2020).

Effects of Psychotropic Medications on Astrocytes in Postmortem Tissue

Few studies have directly examined the effects of antipsychotics and antidepressants on astrocyte expression in human brain. Chronic antipsychotic use is associated with reduced gray and white matter volumes in SCZ patients (Ho et al. 2011), including reductions in gray matter volume in patients administered the antipsychotic haloperidol following first-episode psychosis (Lieberman et al. 2005). Gray and white matter volume changes in SCZ patients may reflect reduced glial cell density or counts induced by antipsychotic medication. There are several reports suggesting no association between antidepressant use and changes in glial density, cell count, or astrocyte marker expression in MDD studies (Ongur et al. 1998; Rajkowska et al. 1999; Cotter et al. 2001a; Torres-Platas et al. 2016; Miguel-Hidalgo et al. 2010), although antidepressant use was correlated with reduced GFAP protein expression in the cerebellum of subjects with MDD (Fatemi et al. 2004). Importantly, many studies were not sufficiently powered to detect a medication effect, and further research will be required to determine the effects of antidepressants on astrocyte expression in MDD. Little is known about the effects of lithium, a first-line treatment for BPD, on astrocyte expression in human brain; however, transcriptomic analysis of mouse astrocytes found lithium-responsive genes in primary cultured mouse astrocytes, suggesting that astrocytes are a direct cellular and molecular target of lithium (Rivera and Butt 2019). Lithium administration also resulted in an increase in astrocyte density in the hippocampus of adult mice (Rajkowska et al. 2016) and induced a highly polarized morphology in mouse ex vivo cultured astrocytes which is typical of reactive astrogliosis (Rivera and Butt 2019). Taken together, these studies raise the possibility that astrocyte expression changes seen in the brain in SCZ, MDD, and BPD may reflect the effects of chronic medication use.

In summary, a growing number of postmortem studies highlight a change in astrocyte morphology and the expression of functionally important astrocyte markers and how they are altered in the brain in neuropsychiatric disorders. Further studies are necessary to provide a greater understanding of the role of astrocytes in the pathophysiology of these disorders and may lead to the development of novel therapeutic targets for these often devastating mental illnesses.

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Astrocyte Bioenergetics and Major Psychiatric Disorders

Ivan V. Maly, Michael J. Morales, and Mikhail V. Pletnikov

Introduction

Recent research has substantially advanced our understanding of the contribution of energy metabolism in neuropathophysiology of major psychiatric disorders and the role of astrocytes in normal and pathological bioenergetics of the brain. Particularly, an appreciation of the essential function of astrocyte metabolism and metabolic regulation in sustaining cognitive activity has emerged from this work. Complementary lines of study continue to document the neurobehavioral consequences of insufficiency of these pathways, which offer valuable models of pathophysiological conditions shared by different mental diseases.

Recent reviews have highlighted the role of astrocytes in synaptic maturation (Augusto-Oliveira et al. 2020), synaptic plasticity and neurotransmission (Augusto-Oliveira et al. 2020; Kim et al. 2018; Roman et al. 2020), neuroinflammation and neurodegeneration (Sofroniew 2020), and interactions with microglia (Liddelow et al. 2020). The present chapter attempts to build on the conceptual foundation laid by the recently published reviews of astrocyte energy metabolism and contributions of astrocyte bioenergetics to neuropsychiatric conditions. While a comprehensive summary of this literature is not possible here, the reader can nevertheless be alerted to the excellent overviews and perspectives on these topics, e.g., by Zuccoli et al. (2017), Sullivan et al. (2018), Takahashi (2020), and Jha and Morrison (2018), as well as those that explore the links to other aspects of brain physiology, such as tissue pH regulation (Deitmer et al. 2019), aging (Morita et al. 2019), and pathological transformation of other glial cell types (Afridi et al. 2020).

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Research into the metabolic role of astrocytes in the brain was presaged by the trophic hypothesis of astrocyte function that, as outlined by Bouzier-Sore and Pellerin (2013), ascends to the views of Camillo Golgi. As originally described, glia was differentiated from neurons by the absence of axons and exclusive presence of dendrite-like protrusions, to which a nutritive function was ascribed. While Santiago Ramon y Cajal did not subscribe to the trophic view, he envisioned (see Mishra 2017) astrocytes as capable of regulating blood vessel diameters. Metabolic cooperation between neurons and astrocytes, suggested by the early microanatomical concepts, found empirical support in the pioneering experiments conducted by Hamberger and Hyden (1963). When stimulated, isolated neurons exhibited an increase in oxidative capacity at the same time as astrocytes elevated their glycolytic activity, implying a division of metabolic labor between the two major cell types in the brain. The present-day picture of neuron-astrocyte cooperation has acquired a significant level of molecular and cellular details that remain broadly compatible with the early insights and conjectures. Similarly, while major psychiatric disorders are now recognized as complex disorders of the multifactorial etiology (Freund and Juckel 2019; Ohi et al. 2020; Zamanpoor 2020), attention to energy metabolism as a contributing factor dates back to the earliest days of modern biochemical research into mental disease (reviewed by Kety 1959). Considering the present-day controversies in a historical, hundred-year-old context provides a useful perspective on the recent studies.

Our review opens with an outline of the astrocytes' participation in the brain metabolism on the organism, organ, and cellular level. We briefly cover the astrocytes' place in the brain-liver circuit of glucose homeostasis and proceed to a discussion of the current model of vascular regulation mediated by calcium signaling and fatty acid metabolites in astrocytes responding to synaptic activity. These organ-level and interorgan mechanisms provide the physiological context for an overview of the neuron-astrocyte cooperation in the neuropil. An attempt is made to offer a description based on the pathway-centric, molecular-biochemical notion of metabolic fluxes in the cell as well as across cell types. We then overview the fundamental energy metabolism processes in relation to the current genetic, epigenetic, and metabolomic data concerning the molecular basis of the major mental disorders and attempt to propose new directions for research and potential therapeutic intervention.

Metabolite-Mediated Interorgan Signaling

The place of brain metabolism in interorgan regulatory axes is an active area of research that has already yielded insights into the pathophysiological mechanisms contributing to major psychiatric disorders. Ongoing research is clarifying the processes whereby energy metabolism in astrocytes is positioned at the crux of blood glucose regulation during normal cognitive activity and in organism-level dysregulation that can impact the course of mental disease. Although it is likely that astrocytes from other brain structures may contribute to these processes through regional

and systemic effects, hypothalamic astrocytes are uniquely positioned to directly influence the brain sensing of blood glucose levels in an interorgan feedback loop (Camandola 2018; Fuente-Martin et al. 2019). Astrocyte-specific uptake of glucose that is mediated by glucose transporter 1 (GLUT1) is critical to glucose-sensing that takes place in the hypothalamic glia (Chari et al. 2011) and complements the glucose-sensing function of hypothalamic neurons (see Fuente-Martin et al. 2019). Elevated glucose causes activation of astrocyte-specific lactate production in the hypothalamus, which fuels adenosine triphosphate (ATP) generation in neurons of the arcuate nucleus (Lam et al. 2005). Activation of hypothalamic ATP-sensitive potassium channels, through the brain-stem projections of the arcuate nucleus and vagal efferents, suppresses gluconeogenesis and glycogenolysis in the liver (Pocai et al. 2005).

A similar process affecting glucagon production appears to be operating through glucose transporter 2 (GLUT2) (Marty et al. 2005), while insulin release by the pancreas in response to elevated glucose exhibits dependence on connexin-mediated cytoplasmic communication between the arcuate nucleus astrocytes (Allard et al. 2014). There is also evidence that astrocytes' ability to catabolize lipids and produce ketone bodies, uniquely among the brain cell types, allows them to modulate the activity of glucose- and lipid-sensing neurons, affecting food intake, particularly in animals fed with a high-fat diet. In these experiments (Le Foll 2019; Le Foll et al. 2014), firing rate of arcuate nucleus and ventromedial hypothalamus neurons was directly affected by ketone bodies characteristically produced by hypothalamic astrocytes. A pathway mediated by lipoprotein lipase appears to play a complementary role (Gao et al. 2017), as a loss of this enzyme in hypothalamic astrocytes leads to suppressed synthesis of lipid droplets in these cells and is accompanied by development of glucose intolerance and weight gain on high-fat diet. Taking into account the association of organism-level metabolic disorder, including diabetes and obesity, with the course and severity of schizophrenia, bipolar syndrome, major depression, and anxiety (Annamalai et al. 2017; Chouinard et al. 2016; Lundqvist et al. 2019), further delineating the role of astrocyte metabolism in organism-level glucose regulation and food consumption behavior represents a potentially fruitful direction.

In addition to the astrocyte-derived metabolites affecting efferent signals to the liver and pancreas, there is an intriguing potential connection between astrocyte metabolism and signaling to the brain by a major gut microflora metabolite, D-lactate. D-lactate can compete with L-lactate produced by astrocytes and transferred to neurons during cognitive tasks, impairing memory formation and synaptic plasticity (Baker and Edwards 2007; Gibbs and Hertz 2008; Murphy-Royal et al. 2020). These observations have been seen as implicating astrocytes in the pathology manifested as D-lactate encephalopathy, a rare condition which can be accompanied by delirium along with other neurological abnormalities. Comporting with this view, diet conducive to D-lactate production in the hind gut of rats and D-lactic acid concentration in the plasma of these animals have been correlated with memory impairment in behavioral studies (Hanstock et al. 2010). Among the potential mechanisms behind the link between gut dysbiosis and mental illness (Bruce-Keller et al.

2018; Rogers et al. 2016), the D-lactate and astrocytes connection deserves further scrutiny in light of the particularly strong association of schizophrenia and bipolar disorder with the *Lactobacillus* species that produce D-lactate, such as *Lactobacillus gasseri* (Dickerson et al. 2017; Nguyen et al. 2018).

Regulation of Vascular Energy Supply

Regulation of energy metabolism on the cell and tissue level in the brain is inseparable from coordination of vascular glucose and oxygen supply that occurs in response to cognitive activity and becomes impaired in neuropsychiatric conditions. Specific cortical regions display dysregulated blood flow in major depressive and bipolar disorder, as well as in schizophrenia (Ota et al. 2014; Sukumar et al. 2020; Wang et al. 2014; Wang et al. 2018; Zhu et al. 2017). These changes are also reflected in the expression of genes involved in vascular regulation and ischemia response (Moises et al. 2015), which are also prominent among genes independently associated with schizophrenia (Schmidt-Kastner et al. 2020). Recent work has begun to unravel the molecular mechanisms whereby local energy supply is regulated by vasoactive compounds released by astrocytes in coordination with the metabolic demands of synaptic transmission. Enveloping both the neuronal synapses and the capillaries, and thus encompassing what is known as neurovascular units, astrocytes are a natural conduit for regulatory information. Future studies of this function of astrocytes in the energy metabolism of the neurovascular units will likely benefit from applications of in vivo imaging of intracellular calcium signaling in astrocytes and adjacent cells using fluorescent sensor proteins, potentially in combination with in vivo functional magnetic resonance imaging (fMRI) now available to rodents (Tsurugizawa et al. 2020).

Astrocytes detect synaptic activity through a palette of transmembrane receptors positioned in immediate proximity of the neuronal synaptic cleft (Haydon 2001; Heller and Rusakov 2017; Stobart and Anderson 2013). Intracellular calcium signals in astrocytes are activated by γ-aminobutyric acid B (Ishibashi et al. 2019; Kang et al. 1998; Meier et al. 2008), muscarinic acetylcholine (Takata et al. 2011), purinergic P2Y (Simard et al. 2003), endocannabinoid (Navarrete and Araque 2010), glutamate (mGluR5), and α-adrenergic and histamine receptors (Bekar et al. 2008; Ding et al. 2013; Shelton and McCarthy 2000; Zonta et al. 2003). Calcium signaling in astrocytes is highly differentiated between regions such as soma, juxtasynaptic protrusions, and end-feet that envelop blood vessels, with intra- and intercellular calcium waves observed upon stimulation and spikes in the end-feet linked directly to the vasomotor effects (Arizono et al. 2020; Chuquet et al. 2007; Howarth 2014; Lind et al. 2013a; Lind et al. 2018; Otsu et al. 2015).

Intercellular propagation of calcium signals may be important for integrated regional responses to neural activity. They are mediated through connexin gap junctions between astrocytes (Gosejacob et al. 2011; Scemes et al. 1998) and the gliotransmitters glutamate, D-serine, and ATP (Bezzi et al. 2004; Harada et al. 2015;

Lalo et al. 2014; Mothet et al. 2005; Volterra and Meldolesi 2005). While mitochondria have been implicated in regulation of the gliotransmitter release (Parnis et al. 2013; Reyes and Parpura 2008; Vardjan et al. 2019), it has been assumed that the calcium-scavenging function of the mitochondrial lumen may be responsible for regulating this process by disrupting the intracellular calcium signal that causes the release. Given that the synthesis of gliotransmitters involved in the intercellular calcium waves is coupled to the energy metabolism, it is possible that their role in wave propagation represents another layer of regulation of this process by the metabolic state of the tissue, whereby a fully mobilized local cell metabolism makes possible a wider regional upregulation of oxygen and glucose supply.

Transmission of signal to the level of intracellular calcium is achieved through inositol trisphosphate release and action on the receptors of the endoplasmic reticulum (InsPR) but also through InsPR-independent action on the intracellular calcium store, as well as calcium-induced calcium release (Okubo et al. 2019; Rodriguez-Prados et al. 2020; Verkhratsky et al. 2012; Volterra et al. 2014). The experiments show that transfer of calcium ions to mitochondria is a particularly robust component of the endoplasmic reticulum-mediated response and can occur even during minor, local calcium release events. The mitochondrial import engages the voltage-dependent anion channel in the outer mitochondrial membrane, which displays calcium ion conductance, and the calcium uniporter in the inner membrane. Absorption of calcium endows mitochondria with an ability to attenuate calcium-mediated signaling in astrocytes (Boitier et al. 1999; Jackson and Robinson 2015; Jackson and Robinson 2018; O'Donnell et al. 2016). This ability is linked to the electrochemical effect of the transmembrane electric potential in mitochondria driving the calcium import and also to the normally occurring repositioning of mitochondria toward the intracellular sites of high energy demand. Conversely, rapid oxidative phosphorylation and the attendant generation of reactive oxygen species propagate the intracellular calcium signal through the induced opening of the permeability transition pore (Agarwal et al. 2017). Thus, recent research suggests that the transmission of the energy-demand signal from the activity in the neuronal synaptic cleft can be subject to modulation by the astrocyte's own metabolic state.

Elevation of intracellular calcium has been linked to the release of vasoactive compounds that include metabolites of arachidonic acid, nitric oxide, potassium, and carbon monoxide (Mahan 2019; Stobart and Anderson 2013). The effects mediated by arachidonic acid are regulated through the calcium dependence of phospholipase A_2 (Sun et al. 2005). Direct action of arachidonic acid on smooth muscle cells is vasoconstrictive and occurs via its conversion, in the target cells, into 20-hydroxyeicosatetraenoic acid (Mulligan and MacVicar 2004). However, elevated activity in the neural tissue causes the parallel pathway to predominate, which are mediated by conversion of arachidonic acid in the astrocytes into prostaglandin E2. The switch is effected by lactate sensitivity of prostaglandin elimination from the extracellular space, which occurs via the prostaglandin-lactate antiporter, and an increased production of lactate by astrocytes in response to tissue energy demands, to be reviewed in detail in the next section. Accumulation of extracellular

prostaglandin E2 is believed to drive vasodilation that is observed under these conditions (Gordon et al. 2008).

By comparison, carbon monoxide (CO) production in astrocytes is stimulated by calmodulin-dependent activation of heme oxygenase (Xi et al. 2011) and can complement the direct action of glutamate on CO generation in the endothelium and vascular smooth muscle (Leffler et al. 2003). It is interesting to note that in addition to its vasomotor effect, CO stimulates mitochondrial metabolism in astrocytes, as well as in neurons (Almeida et al. 2012; Almeida et al. 2016). It is conceivable that this dual function serves to feed back on the energy consumption in the complex tissue when its supply via the local vasculature is ensured. Such a mechanism would comport with the hemo-neural hypothesis (Moore and Cao 2008) and also with the observation that increased arteriole blood pressure triggers calcium signaling in astrocytes, a process mediated by transient receptor potential vanilloid 4 channels (Diaz et al. 2019; Kim et al. 2015b). Perturbation of this signaling pathway in hypertension has been hypothesized to contribute to cognitive decline. Indeed, since hypertension is a frequent comorbid condition in patients with bipolar disorder and schizophrenia (Ayerbe et al. 2018), this potential connection merits further exploration. Overall, the present state of knowledge concerning the astrocytes' place in regulating the vascular energy supply to specific brain regions suggests multiple inputs reading out the state of local metabolism and integrating the signals into the vasomotor response.

Metabolic Fluxes in Gray Matter

Different aspects of the metabolic flux distributions among cell types and pathways in the gray matter of the brain have been subject of comprehensive recent reviews (see, in particular, Barros et al. 2018; Jha and Morrison 2018; Deitmer et al. 2019; Dienel 2019). In addition to qualitative conceptualizations, formal flux balance analysis has been carried out to pinpoint the main features of the energy metabolism in this complex tissue and the role played by different cell types (DiNuzzo et al. 2017; Rothman and Dienel 2019). The chief energy consumer in the brain is the neuronal electrogenic Na^+/K^+ ATPase. The electric current associated with each synaptic event is on the order of nanoampere, yet considerable energy expenditure is required to sustain a frequency of such events that may reach 100 Hz per synapse, when the total number of synapses in the human brain is estimated at 10^{15}. The work associated with synaptic activity, naturally, is added to any basal metabolic demands, in which maintenance of ionic gradients is prominently represented in all cell types. Brain energy metabolism, and particularly that in gray matter, is characterized by its reliance on glucose supply and astrocyte glycolysis to meet rising energy demand that occurs during cognitive tasks.

Pathways of Nutrient Utilization

Discussion of issues pertaining specifically to the current research in astrocyte metabolism and neuropsychiatric conditions can be aided by first revisiting the well-established general features of energy metabolism in gray matter. Glucose in the brain is transported out of the bloodstream by GLUT1 uniporter across the endothelial membranes. The same GLUT isoform is responsible for its uptake into astrocytes (Simpson et al. 2007), whereas neurons express kinetically different GLUT3 and GLUT4, whose presentation on the plasma membrane is sensitive to the energy demand (Ashrafi et al. 2017; Pearson-Leary and McNay 2016). Once in the cytosol, glucose is sequestered by conversion to glucose-6-phosphate by hexokinase. This can be regarded as the first step in glycolysis but also supplies the substrate for the pentose phosphate pathway and glycogen shunts. Glycogen synthesis and degradation cycle is a distinguishing biochemical characteristic of astrocytes, and its role in energy mobilization will be reviewed in detail below. The pentose phosphate pathway is important in the brain for generation of reducing equivalents in the form of nicotinamide adenine dinucleotide phosphate (NADPH). The two molecules of NADPH per glucose molecule shunted to this pathway can be utilized by glutathione reductase to regenerate glutathione consumed in peroxidation that eliminates hydrogen peroxide, the product of both oxygen radical generated during respiration, and monoamine oxidase-catalyzed degradation of neurotransmitters. As both processes are accelerated during cognitive tasks, and in view of the specific link of cognitive decline in schizophrenia to redox imbalance (Maas et al. 2017), a protective role of astrocyte metabolism represents a promising direction of study (Tarasov et al. 2019).

The downstream steps in glycolysis are at the core of astrocyte energy metabolism and also supply precursors for synthesis of neurotransmitters such as glycine, L-serine, D-serine, and others. One major branch of glucose metabolism in astrocytes is the reduction of pyruvate to lactate catalyzed by lactate dehydrogenase, which produces two moles of NADH per mole of glucose. However, the importance of astrocyte lactate generation in different physiological and pathological states continues to be debated, as will be reviewed below (see also Deitmer et al. 2019; Dienel 2019). Fatty acids represent an alternative energy source for astrocytes (see Lee et al. 2020). Their uptake is mediated by fatty acid binding proteins (FABP) that facilitate the transit across cell membranes (Pan et al. 2015; Rapoport et al. 2001; Smith and Nagura 2001). β-Oxidation and entry into the citric acid cycle with acetyl-CoA provide the pathway for fatty acid utilization in the energy metabolism of astrocytes and can substitute for glucose utilization pathways under conditions of glucose starvation (Weightman Potter et al. 2019). During general nutrient deprivation, astrocytes metabolize their lipid reserves contained within cytoplasmic droplets (Cabodevilla et al. 2013). However, as recent research shows, astrocyte fatty acid oxidation also operates in tandem with glycolysis (Eraso-Pichot et al. 2018; Panov et al. 2014). The significance of this process in the brain function is underscored by experiments with the astrocyte-specific FABP7 (Sharifi et al. 2011; Sharifi

et al. 2013). Deletion of the *Fab7* gene in mice affects neurogenesis, neuronal morphology, and synaptic function, as well as pre-pulse inhibition of the acoustic startle that can be impaired in patients with several neuropsychiatric diseases (Ebrahimi et al. 2016; Watanabe et al. 2007). Further work is needed to more fully uncover the contribution of lipid metabolism in astrocytes to etiology of major psychiatric disorders.

Intercellular Transport of Metabolites

The energy metabolism pathways display a marked differentiation between neurons and astrocytes, leading to establishment of intercellular fluxes and metabolic cycles. There are three major metabolite exchange mechanisms mediated by lactate, glutamate, and γ-aminobutyric acid (GABA). The latter two specifically engage glutamatergic and GABAergic neurons and are directly linked to synaptic neurotransmission. By comparison, lactate exchange is believed to involve all neuronal cell types. In order to set the stage for discussion of these critical issues that may impact the interpretation of genetic associations of metabolic factors with neuropsychiatric disease, it is worth describing the current understanding of how the intercellular fluxes are organized and integrated into the intracellular pathways characterizing neurons and astrocytes.

The turnover of glutamate and its role in schizophrenia is reviewed in the preceding chapter. Certain metabolic connections of the fate of glutamate that is released in neurotransmission, nonetheless, deserve mentioning here. Although neurons express neuronal glutamate symporters, the majority of glutamate is recovered from the extracellular space surrounding the synaptic cleft by astrocytic symporters, glutamate aspartate transporter 1 (GLAST-1), and glutamate transporter 1 (GLT-1), a.k.a. excitatory amino acid transporter 1 and 2 (Pellerin and Magistretti 1994; Pines et al. 1992; Shashidharan et al. 1994; Storck et al. 1992). Inside astrocytes, glutamate is oxidized to α-ketoglutarate by either glutamate dehydrogenase or aspartate aminotransferase (Faff-Michalak and Albrecht 1993; McKenna et al. 2006a), which diverts 20–30% of the synaptic glutamate to the Krebs cycle (Dienel 2019; Stobart and Anderson 2013). Glutamate can also by synthesized de novo from α-ketoglutarate. Regardless of its source, glutamate in astrocytes is subject to conversion to glutamine (Martinez-Hernandez et al. 1977) before it can be exported back into the extracellular space. After its uptake by the neuron, glutamine undergoes deamidation inside the mitochondria to produce glutamate that is then accumulated in presynaptic vesicles. Oxidation of glutamate and entry the citric acid cycle in astrocytes serve to recover the energy expended by in its import, which dissipates the electrochemical gradient of sodium across the astrocytic plasma membrane. An interesting recent finding concerning lipid utilization in astrocytes is its downregulation by glutamate (Eraso-Pichot et al. 2018), which suggests a potential for substitution of the energy derived from fatty acid oxidation by the entry of glutamate into the citric acid cycle. The GABA shuttle operates similarly and

overlaps with the glutamate-glutamine cycle due to the production of this inhibitory neurotransmitter from glutamine in GABA-ergic neurons and its entry into the astrocytic Krebs cycle via succinic semialdehyde and succinate (Cooper and Jeitner 2016; Dienel 2019).

Recent research has focused on the exchange of lactate and glutamate between neurons and astrocytes and on the role of these processes in coordination of energy metabolism between the cell types in gray matter. The role of the extracellular lactate in the astrocyte metabolism was highlighted by the observation that astrocytes in culture secrete lactate when grown in glucose-containing medium and then consume the lactate from the medium as the glucose is exhausted (Lind et al. 2013b). In contrast to neurons, which import lactate via monocarboxylate transporter 2 (MCT2), astrocytes utilize MCT1. Export of lactate from astrocytes has been associated with MCT4 (Bergersen et al. 2001; Chiry et al. 2008; Mazuel et al. 2017; Pierre and Pellerin 2005). Up to one-half of the glucose is converted to extracellular lactate in astrocytes, as well as in cortical and cerebellar glutamatergic neurons under both resting and depolarizing conditions (Gebril et al. 2016; Jekabsons et al. 2017; Lopes-Cardozo et al. 1986; Waagepetersen et al. 2000). Computational kinetic analysis suggests that the net transport between astrocytes and neurons in vivo accounts for only 2% of the taken-up glucose equivalents and for 11% of accelerated glucose consumption (Mangia et al. 2011). Thus, there may be a large difference between the intensity of the lactate exchange and the small magnitude of its directional flux, considered in relation to the overall rate of metabolism in the astrocyte-neuron system. These kinetic observations about the magnitude of flux, however, do not preclude lactate from performing an important function; rather, they are consistent with the emerging view that lactate is part of a redox buffer that equilibrates NAD^+/NADH ratio among cells in the tissue (Rabinowitz and Enerback 2020).

Flux Redistribution in Response to Demand

Redistribution of metabolic fluxes among the cells of gray matter that sustains a rise in neuronal activity is an active area of research. Several themes are emerging, which highlight, in particular, the role of astrocytic glycogen, malate-aspartate shuttle regulation, and the relative weight of the flux through the pentose phosphate shunt. Notable features that differentiate metabolism of neurons from astrocytes are low-level glycogenic enzymes and the usual absence of glycogen in neurons (cf. Saez et al. 2014; Sotelo and Palay 1968). Glycogen turnover in the brain is tightly regulated, and in the extreme case of pathology of this process, its dysregulation in Lafora disease can be fatal (Obel et al. 2012; Roach 2015). Supporting the central role of this energy depot in astrocytes, experimental knockout of glycogen synthase causes impairment of memory formation (Duran et al. 2013). The energy flux from glycogen is also crucial for maintaining the astrocytes' ability to scavenge potassium and accumulate calcium ions in their intracellular stores (Muller et al. 2014;

Xu et al. 2013). It has been suggested that glycogenolysis in astrocytes is subject to monoamine regulation (Dienel and Cruz 2015; DiNuzzo et al. 2015), which would account for accumulation of glycogen in the absence of stress (Cruz and Dienel 2002; Kong et al. 2002b; Oe et al. 2016), and its rapid utilization, amounting to half of the blood glucose uptake, which can be triggered by sensory stimulation (Dienel 2019; Dienel et al. 2002). Similarly, access to glucose following a period of utilization of glycogen in astrocytes leads to establishment of a significant glucose uptake rate as the glycogen store is replenished (Walls et al. 2009). Overall, while the studies continue, it is clear that the glycogen energy buffer in astrocytes makes a large contribution to the metabolic fluxes that precede, accompany, and follow functional activation of gray matter, and it is critical to performance in cognitive tasks.

Scavenging of NADH through the malate-aspartate shuttle is required for continued operation of the glycolysis pathway, when pyruvate enters the citric acid cycle. Interestingly, there is evidence that the shuttle is inhibited by Ca^{2+} fluctuations that exceed the threshold concentration characterizing the mitochondrial calcium uniporter in neurons, redirecting the pyruvate flux to lactate production in the cytosol (Satrustegui and Bak 2015). The lactate may then become redistributed across the activated region of gray matter through gap junctions that connect the region's astrocytes in a functional syncytium (Hertz et al. 2014). Loss of any excess lactate into the bloodstream would account for the submaximal oxygen-glucose index, whose fall in activated brain regions is well documented, reflecting incomplete oxidation of carbon taken up with glucose (Juaristi et al. 2019). Compared to neurons, expression of the malate-aspartate transporter AGC1 is lower in astrocytes (Pardo et al. 2011) and does not appear to be critical for glucose oxidation (Juaristi et al. 2017). Instead, the transport of reducing equivalents to mitochondria in stimulated astrocytes appears to be mediated largely by the glycerol phosphate shuttle, whereby the cytoplasmic glycerol-3-phosphate dehydrogenase oxidizes NADH to reduce dihydroacetone phosphate and the mitochondrial isoform oxidizes this substrate to produce $FADH_2$ (Juaristi et al. 2017). These findings are consistent with the results of the pharmacological approach to differentiating between the transporter systems (Kohler et al. 2018; McKenna et al. 2006b). Mitochondrial glycerol-3-dehydrogenase is activated by calcium from the outer side of the inner mitochondrial membrane and generates large amounts of hydrogen peroxide, which distinguishes mitochondrial respiration in astrocytes (Tretter and Adam-Vizi 2012). The demonstrated involvement of different calcium-regulated transport systems in the neuronal and astrocytic mitochondria suggests that the neuronal-astrocytic metabolic cooperation may be orchestrated by coordinated calcium signals in the two cell types. Microanatomical characterization of the astrocyte-neuron contacts, whereby a single branch of an astrocyte can engage with hundreds of synapses, along with the most recent discovery of local calcium signals in subcellular domains of astrocytes, has led to a hypothesis that the local calcium signals read out the local (subcellular) activity levels in groups of synapses, causing a localized metabolic response (Oheim et al. 2018). Advances in optical registration of calcium signals in vivo and simultaneous visualization of such subcellular parameters as NAD redox status and mitochondrial motility have the potential to clarify these issues.

Most recent work demonstrates existence of a lipid flux from neurons to astrocytes induced by neuronal activity. It has been known for some time that activated neurons generate excess fatty acids that may be peroxidized by reactive oxygen species (Reynolds and Hastings 1995; Sultana et al. 2013). Recent data show that peroxidized fatty acids in neurons follow a pathway that takes them from autophagocytosed membranes to lipid droplets (Ioannou et al. 2019). In agreement with the previously demonstrated low capacity of neurons for fatty acid utilization (Schonfeld and Reiser 2017), excess fatty acids are transported to neighboring astrocytes in dense carriers containing apolipoprotein E (Ioannou et al. 2019). Furthermore, glutamate released by the activated neurons stimulates both lipolysis and reactive oxygen species neutralization in the astrocytes. These findings elaborate on the earlier demonstration that oxidative stress in neurons is accompanied by accumulation of lipid droplets in adjacent astrocytes in a manner that is dependent on apolipoproteins (Bailey et al. 2015; Liu et al. 2015; Liu et al. 2017). More work is needed to elucidate the possible connections of this metabolic flux with psychiatric disorders, but given the well-documented involvement of neuronal oxidative stress in their etiology and progression (e.g., Flatow et al. 2013; Fraguas et al. 2017), this represents a promising direction for future research.

In culture, glutamatergic cerebellar neurons preferentially metabolize glucose over lactate when subjected to stimulation (Bak et al. 2006). The implications of this preference for the in vivo situation, where NADPH generated in the pentose phosphate pathway participates in amelioration of oxidative stress, have been disputed in view of the competition of glycolysis with the pentose phosphate shunt for glucose-6-phosphate. A key finding supporting upregulation of lactate utilization instead of glycolysis is the inability of neurons to increase the activity of phosphofructokinase 1, the gatekeeper of the specifically glycolytic energy-producing flux (Bolanos 2016; Herrero-Mendez et al. 2009). The regulation depends on production of fructose-2,6-bisphosphate, a critical phosphofructokinase 1 activator, which is catalyzed by 6-phosphofructo-2-kinase. This enzyme was found at low levels in the cultured and ex vivo neurons, compared with astrocytes, and its experimental overexpression directed the glucose flux into the glycolytic pathway at the expense of the pentose phosphate shunt. In neurons, this intervention led to lethal oxidative stress. However, other conditions, in which cultured neurons and isolated synaptic regions have been studied, demonstrated glycolysis upregulation, increased glucose use, and elevated surface expression of glucose transporters (see Dienel 2012; Patel et al. 2014). Moreover, stimulation of brain slices and the whisker barrel cortex in vivo leads to upregulation of neuronal glycolysis accompanied by lactate production, instead of uptake (Diaz-Garcia et al. 2017). These disparate observations—or, rather, interpretations that emphasize the glycolysis and pentose pathway activation—can be reconciled by recalling that fructose-6-phosphate produced in the pentose shunt can be recycled through its conversion to glucose-6-phosphate, while glyceraldehyde-3-phosphate can feed the downstream, energy-producing steps of glycolysis (Dienel 2019). This leads to a picture whereby levels of brain matter activation that do not fully engage glycogenolysis may be accompanied by a more bidirectional energy flow between neurons and astrocytes. Whereas the details of

metabolic flux regulation attendant to performance of cognitive tasks continue to emerge from ongoing fundamental research, the clear importance of glycogen turnover, calcium signaling regulation of lactate production, and the pentose phosphate shunt in astrocytes can inform the interpretation of data from molecular studies of pathology in major psychiatric conditions.

Metabolic Disorders and Neuropsychiatric Disorders

As reviewed above, astrocytes represent an indispensable link in brain metabolism and organism-level regulation of energy supply to the brain. The studies on normal tissue demonstrate that metabolite-mediated interaction of astrocytes and neurons and signal propagation across the cell types in the brain are central to the exquisitely orchestrated physiological adaptation to increased neuronal activity and synaptic transmission. This physiological and biochemical information allows us to interpret the genomic, metabolomic, and expression data that document the involvement of metabolism in neuropsychiatric disorders.

Our present understanding of the molecular mechanisms underlying the core symptoms of schizophrenia and other major psychiatric disorders focuses on abnormalities in synapse development and synaptic communication (Duman et al. 2016; Frankle et al. 2003; Keshavan et al. 2020; Lee et al. 2018; Mirnics et al. 2001; Stephan et al. 2009). Comporting with this primarily developmental view, mice produced with glial progenitors derived from childhood-onset schizophrenia displayed, in particular, delayed astrocytic differentiation (Windrem et al. 2017). Notably, inhibition of SMAD signaling can both rescue the differentiation process and lead to normalization of potassium transport in the affected glia (Liu et al. 2019). These new data are consistent with the involvement of potassium transport both on the level of small conductance calcium-activated potassium channels ($K_{Ca}2.3$), encoded by the *KCNN3* gene that is associated with the 1q21-q22 locus linked to familial schizophrenia (Brzustowicz et al. 2000), and the sodium/potassium-transporting ATPase subunit α-3 encoded by *ATP1A3*, which has been linked to childhood-onset schizophrenia (Smedemark-Margulies et al. 2016).

Postmortem Evidence

Similarly, studies in human postmortem prefrontal cortex of patients with schizophrenia have detected abnormalities in the composition and distribution of the astrocytic metabolon (Genda et al. 2011) that involves glutamate transporters, hexokinase-1, and sodium/potassium-transporting ATPase, including apparent spatial uncoupling of the molecules from mitochondria (McCullumsmith et al. 2016; Shan et al. 2014). As altered glutamate turnover is implicated in schizophrenia and could represent a vital link between the neuronal and astrocytic metabolism (Section

"Intercellular Transport of Metabolites"), with the maintenance of membrane potential the leading energy expenditure, these findings suggest that it will be particularly important to investigate further the role of astrocyte energy metabolism in the pathogenesis and/or pathophysiology of this disease (Sullivan et al. 2018). Of special note is decreased expression of glial fibrillary acidic protein (GFAP), a major astrocyte marker, on astrocytes in close contact with blood vessels, suggesting changes in uncoupling of glucose energy supply within the affected neurovascular units (Webster et al. 2001). Furthermore, major depression is accompanied by downregulation of glutamate transporters along with glutamine synthase and connexins, the characteristic astrocyte proteins involved in maintaining the integrity of the glutamate-scavenging functional syncytium (Bernard et al. 2011; Blomstrand et al. 1999; Choudary et al. 2005; Sequeira et al. 2009; Zhou et al. 2019). Recent postmortem evidence also suggests impairment of glucose metabolism in the striatum of certain patients with schizophrenia (Dean et al. 2016), while both glycogen phosphorylase and its regulatory kinase are downregulated in dorsolateral prefrontal cortex astroglia of chronic patients (Pinacho et al. 2016). Thus, although our understanding of the involvement of astroglia in the developmental pathology of major psychiatric disorders can be characterized as nascent, it is already beginning to supply mechanistic hypotheses for how dysregulation of energy metabolism could affect these processes.

Genetic Evidence

Schizophrenia is a condition notable for its heritability, and genome-wide association studies have identified variations in over 100 loci linked with the disease (Pardinas et al. 2018; Schizophrenia Working Group of the Psychiatric Genomics 2014). Large and small de novo copy number variations have high penetrance and affect functionally diverse proteins (Fromer et al. 2014; Tansey et al. 2016). Enzymes of the glycolytic pathway, including the regulatory 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2, the flux-controlling hexokinase 3, and pyruvate kinase 3, were found to be specifically associated with development of schizophrenia (Stone et al. 2004). Glycolysis and citric acid cycle genes are also prominent among the single-nucleotide variants associated with bipolar disorder, a similarly heritable condition (Ament et al. 2015). Although some of these associations are tentative and dependent on other conditions such as the patient's race, due to their inherent nature, genetic data pointing to involvement of metabolic alterations in major psychiatric disorders have the advantage of not being impacted by the complicating developmental and environmental factors such as diet or side effects of antipsychotic medication, whose role will be reviewed below. Although existing evidence suggests that genetic risk variants may be responsible for metabolic disturbances in many psychiatric disorders, what remains unknown is whether these risk variants affect metabolic pathways or functions predominantly in neurons or also in non-neuronal brain cells and/or other tissues.

Gene Expression and Functional Data

On the gene expression level, recent work has identified functional gene sets that exhibit dysregulated levels in autism, bipolar disorder, and schizophrenia (Guan et al. 2019). The enriched sets include amino acid transport, neurotransmitter release, oxidative stress response and immune response, and also mitochondrial proteins and glycolysis. Meta-analysis of proteomic data from post-mortem brain material shows in excess of 90 differentially expressed energy metabolism genes in bipolar disorder and schizophrenia and 40 in major depressive disorder (Zuccoli et al. 2017). All three conditions implicate aldolase C, the central enzyme in glycolysis, citrate synthase and malate dehydrogenase of the citric acid cycle, cytochrome b-c1 subunit 1, and the β-subunit of ATP synthase. Intramitochondrial pyruvate dehydrogenase, aconitase, isocitrate dehydrogenase, and 2-oxoglutarate dehydrogenase of the citric acid cycle and several additional components of the electron transport chain are also affected, as are pyruvate kinase, enolase, glyceraldehyde-3-phosphate dehydrogenase, and phosphofructokinase 1 of the glycolytic pathway. These recent analyses are broadly in agreement with the targeted proteomic, transcriptomic, and functional approaches that detected alterations in glycolysis, citric acid cycle, and the respiratory chain in specific brain regions of patients with schizophrenia and other major psychiatric disorders (Beasley et al. 2006; Beasley et al. 2009; Bubber et al. 2011; Cavelier et al. 1995; Du et al. 2014; Martins-De-Souza et al. 2009a; Martins-De-Souza et al. 2009b; Maurer et al. 2001; Middleton et al. 2002; Pennington et al. 2008; Prabakaran et al. 2004; Stork and Renshaw 2005).

Similar to the genetic insights, the bulk tissue expression data is unable to identify cell-type specific metabolic alterations. Moreover, any compensatory changes across cell types would not be reflected in the bulk tissue results. Laser capture and microdissection have been used to assess changes specific to neurons, particularly in granule cells of the dentate gyrus and prefrontal pyramidal cells (Altar et al. 2005; Arion et al. 2015; Arion et al. 2017). In the hippocampus, schizophrenia patients were distinguished from bipolar and major depression cohorts by decreased expression of isocitrate, lactate, malate, NADH, and succinate dehydrogenases, as well as cytochrome C oxidase and ATP synthase. The pyramidal cells showed downregulation of mitochondrial energy metabolism genes in the schizophrenia samples with no alterations being observed in samples from patients with the bipolar disorder, major depressive disorder, or schizoaffective disorder. The technique has also been applied to study alteration of expression of astrocytic genes in specific layers of the anterior cingulate gyrus and revealed downregulation of glutaminase and excitatory amino acid transporter 2 in postmortem material from patients with schizophrenia (Katsel et al. 2011a). More cell type-specific data are necessary to form a clear picture of the metabolic alterations at the cellular level in mental illnesses.

Effects of Antipsychotic Medications

Studies on drug-naïve patients with psychiatric illnesses support the notion that the metabolic alterations are inherent in these conditions. For example, impaired glucose tolerance and metabolic syndrome are associated with first-episode schizophrenia or psychosis (Chen et al. 2016a; Perry et al. 2016; Petrikis et al. 2015; Pillinger et al. 2017; Ryan et al. 2003; Spelman et al. 2007; Zhang et al. 2015b). In the case of first-episode psychosis, however, negative findings have also been reported (Sengupta et al. 2008). By contrast, in a different study on drug-naïve patients, it was found that 8 out of 18 differentially expressed genes in peripheral monocytes of antipsychotic-naïve patients were from the glycolytic pathway (Herberth et al. 2011). Positron emission tomography demonstrates that drug-naïve patients with schizophrenia display an increased variation of glucose metabolic rates about the mean, compared with the healthy controls. This increased variation was observed in a number of different brain regions (Wiesel et al. 1987). At the same time, chronic patients show a decreased level of glucose metabolic rates. Region-specific reduction in glucose metabolism is seen in the hippocampus and anterior cingulate cortex (Tamminga et al. 1992). Despite the availability of data from drug-naïve patients, widespread and chronic use of antipsychotic drugs confounds the efforts to determine whether metabolic disturbances are the primary contributing factors or consequences of treatments that could influence the course and severity of the disease. Positron emission tomography, on the other hand, showed that haloperidol enhanced glucose utilization in the caudate and putamen, while lowering it in the anterior cingulate and frontal cortex (Holcomb et al. 1996). A more recent study has addressed the effect of a combined aripiprazole-amisulpride therapy and found glucose metabolism to be accelerated in the right superior frontal and frontal precentral gyri (Park et al. 2019).

The impact of antipsychotic medication on cell metabolism is well documented in vitro. Haloperidol, clozapine, chlorpromazine, and fluphenazine all suppress glucose uptake in experiments on PC12 cells following their administration but cause what appears to be a compensatory upregulation of GLUT1 and GLUT3 after a longer exposure (Dwyer et al. 1999). In the same neuronal model cell line, as well as in the putamen and caudate nucleus of mice, clozapine acted by reducing signaling downstream of insulin receptor, particularly rendering the phosphorylation of Akt insulin-independent (Panariello et al. 2012). The action of antipsychotic phenothiazines is not limited to their receptor- and cell type-specific interactions but can also be mediated by incorporation into the plasma membrane, as has been demonstrated in experiments on yeast, where they similarly caused inhibition of hexose transporters (Uesono et al. 2016). Further demonstrating that these effects may not be cell-type specific are the similar results obtained following in vitro exposure of a human leukemia cell line (Heiser et al. 2006). Haloperidol treatment of oligodendrocytes led to a higher concentration of glucose and a lower concentration of lactate in the extracellular medium, whereas the atypical antipsychotic clozapine had the opposite effects and, in addition, enhanced oxidative phosphorylation (Steiner

et al. 2014). At the same time, the complexity of psychotropic drug action on the organ level is underscored by the outcome detected in a comparison of the clozapine and haloperidol effects after chronic administration to mice, which showed that mRNA expression related to the carbohydrate metabolism was more affected by clozapine treatment than by haloperidol (Rizig et al. 2012). A number of recent studies suggest that clozapine has a profound effect on mitochondrial functions (Contreras-Shannon et al. 2013; Scaini et al. 2018; Viana et al. 2020). Determining the place of astrocytes in the modulation of brain metabolism brought about by the chronic use of antipsychotic medications is an important direction for future work. Thus, existing data indicate that the action of antipsychotics is highly region-specific and therefore likely to be specific to the regional subtypes of neuronal and glial cells. Further deciphering this complexity of cell-specific action may be necessary for the progress in determining the contribution of astrocyte metabolism to the etiology and progression of the major neuropsychiatric conditions.

Insights from Animal Models

Pharmacological Models

Animal and cell models hold out a promise to permit disentanglement of the genetic, functional, and medication-induced contributions to the etiology of major psychiatric disorders, as well as supply material for the study of cell type-specific effects in these processes. In this section, we will cover what is known about metabolic alterations arising in different types of animal models and attempt to identify the gaps where such knowledge is lacking but where other related data make research advances likely.

Metabolic alterations are consistently observed in *N*-methyl-D-aspartate receptor (NMDAR) antagonist models of schizophrenia. Metabolomic assessment of the cortex and hippocampus in rats treated with MK-801 showed downregulation of glutamate metabolism and the citric acid cycle and, particularly, alterations in the content of citrate and succinate in addition to glutamate and glutamine (Sun et al. 2013). At the same time, a combination of methods revealed a pronounced reduction in glycolysis, "which" was constrained to the parietal and temporal cortex, and highly region-dependent reductions in fumarate and malate turnover (Eyjolfsson et al. 2011). The chronic phencyclidine rat model, by comparison, displays decreased pyruvate and pyruvate kinase levels in the animals' frontal cortex, along with alterations in the glutamate calcium signaling pathway, including calcium-calmodulin-dependent kinase II and calcineurin (Wesseling et al. 2013). Administration of ketamine similarly leads to acute alterations in glycolysis, the pentose phosphate pathway, and citric acid cycle in the hippocampus of mice (Weckmann et al. 2014).

Interestingly, in vitro investigation on neuronal, oligodendrocyte, and astrocyte cell lines demonstrates that the glycolysis inhibition effect of MK-801 is seen in all

three cell types, with the oligodendrocyte glia exhibiting the largest reduction in the glycolytic enzyme expression (Guest et al. 2015). Thus, although it is clear that astrocyte metabolism contributes to the changes seen in vivo—at least with MK-801—its exact contribution to the pathology modeled with the NMDAR inhibitors remains to be determined. It can be noted that NMDAR knockdown in mice also leads to significant changes in key enzyme and calcium signaling molecule expression, including mitochondrial pyruvate kinase, aspartate aminotransferase, and calcium-calmodulin-dependent protein kinase II in the frontal cortex and hippocampus (Wesseling et al. 2014). Together with the effects triggered by administration of NMDAR inhibitors, effects that arise in this genetic model of synaptic disfunction in schizophrenia and autism spectrum disorders argue in favor of the notion that metabolic changes may be triggered downstream of the disrupted NMDAR signal transmission (Sullivan et al. 2018).

Use of dopamine enhancers such as amphetamine and apomorphine remains an informative approach in animal models of schizophrenia (Brisch et al. 2014; Lindenmayer et al. 2013; Winship et al. 2019). Whether astrocyte energy metabolism is involved in the linkage between dopamine dysregulation and its behavioral effects, however, it still unknown. Mitochondrial localization of monoamine oxidase, the dopamine-metabolizing enzyme (Edmondson et al. 2009; Schnaitman et al. 1967), including the one expressed in brain astrocytes (Levitt et al. 1982; Mallajosyula et al. 2008), is suggestive of a possible existence of connection to metabolism. Indeed, in most recent experiments on neurons, it has been demonstrated that dopamine oxidation can supply electrons directly to the mitochondrial transport chain (Graves et al. 2020). It is not clear how these new findings should be reconciled with earlier results obtained on isolated brain mitochondria, where dopamine suppressed pyruvate- and succinate-dependent oxidative phosphorylation and respiration, as well as with inhibition of complex I activity that accompanies elevated dopamine levels induced by chronic administration of *L*-DOPA and *D*-methamphetamine (see Ben-Shachar 2002). Directly addressing the possible role of similar mechanisms in astroglia may be of interest in further studies utilizing the dopamine pharmacological models.

Links to astrocyte energy metabolism have been established more firmly in 5-hydroxytryptophan (5-HT) pharmacological models, although new research is needed to clarify the connecting mechanisms and their influences on behavior. Decrease of astrocytic expression of 5-HT_{2B} receptor is observed in parallel with the progression of the depressive phenotype in a murine model of Parkinson's disease (Zhang et al. 2015a). Because of the frequent presentation with depressed mood among schizophrenia patients (Fortunati et al. 2015), the result just mentioned, which implicates specifically 5-HT signaling in astrocytes, can be directly relevant to modeling schizophrenia in the mouse using deletion of the 5-HT receptor gene or, alternatively, administration of this receptor's inhibitors (Chen et al. 2016b; Pitychoutis et al. 2015). Adding to the evidence for the importance of astrocyte 5-HT signaling are the data concerning administration of 5-HT receptor stimulants and serotonin-specific reuptake inhibitors used in alleviating major depression, such as fluoxetine (Diaz et al. 2012; Li et al. 2008; Qiao et al. 2016; Zhang et al. 2010).

Astrocytic but not neuronal 5-HT_{2B} receptor becomes upregulated under the conditions of chronic treatment with fluoxetine (Hertz et al. 2015; Li et al. 2012). It has been known for some time that fluoxetine, acting via 5-HT_{2B} and intracellular calcium, can stimulate glycogenolysis in astrocytes (Allaman et al. 2011; Chen et al. 1995; Kong et al. 2002a). More recently, it has been established that blocking glycogenolysis prevents serotonin- or fluoxetine-induced memory enhancement (Gibbs and Hertz 2014). The results obtained in culture or on brain slices are in concordance with the earlier observations made on the rat brain, where activators of 5-HT(2) receptor led to a significant downregulation of glycogen and elevation of extracellular glucose (Darvesh and Gudelsky 2003). Evidently, the involvement of astrocyte energy metabolism in mechanisms of major psychiatric disorders will benefit from further studies in 5-HT pharmacological models.

Neuroinflammatory Models

Maternal immune activation models have shown great potential in the study of etiological factors of psychiatric disorders (Careaga et al. 2017; Winship et al. 2019). Infection and other environmental exposures during pregnancy have been associated with schizophrenia, autism spectrum disorders, and bipolar disorder in the offspring, while data from animal models have helped connect the action of cytokines on the fetal brain with behavioral abnormalities in subsequent development. In the animal model approach, immunogens such as polyinosinic-polycytidylic acid, poly(I:C), and lipopolysaccharide (LPS) are employed for triggering maternal immune system response (Conway and Brown 2019).

Numerous lines of evidence implicate astrocytes in the pathological mechanisms triggered by maternal immune activation. Rat astrocytes, but not neurons, secrete tumor necrosis factor α (TNFα) in response to toll-like receptor (TLR) stimulation by LPS, which acts through TLR4, and poly(I:C), which acts through TLR3 (Chistyakov et al. 2018). Poly(I:C), in addition, triggers lysosomal ATP release and intracellular calcium elevation by activating TRPML1 channels in the affected astrocytes (Beckel et al. 2018). A modulating role of the astrocyte energy metabolism in these responses is suggested by most recent experiments that evaluated the activation of p38, JNK, and ERK signaling pathways in astrocytes under conditions of different glucose availability (Bellaver et al. 2015; Chistyakov et al. 2019). The release of TNFα in response to either poly(I:C) or LPS was enhanced in high glucose (25 mM), whereas the kinases were modulated reciprocally and in a time-dependent manner. These intriguing findings are in agreement with the general notion of connection of metabolism to inflammation in the brain (Ristow 2004) and with other recent investigations of modulation of astrocyte signaling by the metabolic conditions (Gandhi et al. 2010; Quincozes-Santos et al. 2017; Wang et al. 2012). Regulation of astrocyte morphology and connexin expression by LPS (Debarba et al. 2019) may also be of relevance to brain metabolism, considering the role of astrocyte connectivity in the spatial organization of neurovascular units

(Section "Regulation of Vascular Energy Supply"). Furthermore, data are beginning to accumulate that describe changes in astrocyte mitochondrial morphology and function under the conditions of inflammatory challenge, for example, with LPS. Impairment of the mitochondrial membrane potential, ATP production, and mitochondrial transcription are among the observed effects (Peng et al. 2019; Zhao et al. 2017). At the same time, the cited data point to a protective role of uncoupling protein 2. More work is needed to elucidate the role of astrocyte energy metabolism in regulating the responses triggered in the organism by maternal immune activation.

The possibility that inflammation signaling in astrocytes may be modulated by energy metabolism is suggested by recent work on the mitochondrial antiviral pathway (Koshiba 2013; Refolo et al. 2020). This pathway is triggered by retinoic acid inducible gene 1-like receptor (RLR), which, alongside the toll-like receptor, has the capacity to recognize double-stranded RNA (see Chattopadhyay and Sen 2014) and signals to membrane-associated mitochondrial antiviral signaling (MAVS) protein. *O*-linked *N*-acetylglucosamination of MAVS in myeloid cells regulates this protein's function (Song et al. 2019) in a manner that depends on the activity of the hexosamine biosynthesis pathway, providing a link between glucose metabolism and antiviral innate immunity (Li et al. 2018). Indeed, in experiments on various cell types, MAVS has been demonstrated to directly sense lactate and associate physically with hexokinase, mediating interferon production-suppressing effect of lactate (Zhang et al. 2019). Conversely, RLR activation suppresses production of glucose metabolites, including lactate, and upregulates MAVS-mediated production of type-1 interferon. This mechanism is compatible with the earlier demonstrated impairment of the MAVS-dependent interferon production, when mitochondrial oxidative phosphorylation is suppressed (Yoshizumi et al. 2017). In light of the recent findings that astrocytes are an important source of interferon produced by the MAVS-mediated pathway (Clarke et al. 2019; Giovannoni and Quintana 2020; Vaccari et al. 2012), it is conceivable that regulatory pathways similar to the ones described in other cells may operate in astrocytes as well and play a role in the neuroinflammatory etiology of autism and schizophrenia.

A new direction of research benefiting from the use of maternal immune activation models targets the role of microbiome in the etiology of major psychiatric disorders. Microbiome imbalance has been implicated in both behavioral abnormalities and immune dysfunction and, particularly, in the abnormal immune function that is associated with autism spectrum disorders (Conway and Brown 2019; Cryan and Dinan 2015; Hsiao 2013). It has been established that the relationship between gut microbiota and neuroinflammation is bidirectional, with the microbiota composition affecting regional immune responses in the brain and being itself regulated by neuroinflammation (Cryan and Dinan 2015; Erny et al. 2015). Remarkably, maternal immune activation in the animal models impacts the immune responses and microbiome composition in the offspring (Hsiao et al. 2013; Kim et al. 2017; Mandal et al. 2013). Among the important questions that remain to be investigated is how astrocyte metabolism may be affected in the enteric nervous system and what role it may play in the lasting changes that develop in the gut microbiota, neuroinflammation, and behavior following maternal immune activation. The connections

of enteric glia and specifically enteric astrocytes with both neurons and immune cells of the intestine are attracting attention in other lines of study, for example, in pain research (Grubisic and Gulbransen 2017; Morales-Soto and Gulbransen 2019). There is evidence for involvement of both gut microbiota and immune system in postnatal development of the enteric nervous system (Bistoletti et al. 2019; De Vedder et al. 2018; Kabouridis and Pachnis 2015), and applications of imaging and optogenetics to target specific cell types of the enteric nervous system in situ are being developed (Boesmans et al. 2018). These advances make it both feasible and imperative to address the question of the possible involvement of enteric nervous system astrocyte energy metabolism in the pathogenesis of behavioral changes triggered by maternal immune activation.

Clues from Models of Substance Use Disorders

Substance use disorders present certain behavioral pathology that is shared with other major psychiatric conditions, and their animal models, as well as in vitro experiments motivated by their study, have great potential to inform our general understanding of the role of astrocyte energy metabolism. Much relevant data also come from research into the effects of specific substances of abuse on primary astrocytic cultures. The chapters that follow in this volume cover the involvement of astroglia in the mechanisms of addiction and alcohol dependence in detail; here, we will maintain our focus on bioenergetics and highlight the data that point at commonality of its perturbation with that in other major psychiatric disorders.

Investigations on mouse brain slices revealed that activation of endocannabinoid CB1 receptors on hippocampal astrocytes leads to calcium release from the intracellular stores, followed by release of glutamate that can act on neuronal NMDAR and potentiate synaptic transmission (Navarrete and Araque 2008, 2010). This insight has led to CB1 signaling being implicated in the disruption of working memory formation by exogenous cannabinoids in vivo (Han et al. 2012). At the same time, it is noteworthy that in both cortical and hypothalamic astrocytes, CB1 signaling sustains the expression of leptin receptors and thus may be linked to regulation of glycogen storage (Bosier et al. 2013). This process may be crucial to address the apparent imbalance between glucose uptake, which tetrahydrocannabinol inhibits in rat brain (Miederer et al. 2017), and glucose metabolism, which this compound upregulates in cultured astrocytes (Sanchez et al. 1998). Furthermore, preadolescent exposure to tetrahydrocannabinol in rats reduces the expression of glutamate synthase (Suarez et al. 2002), which has the potential to perturb the metabolic fluxes associated with the neuron-astrocyte glutamate-glutamine cycle. The specific mechanisms behind the involvement of the astrocyte energy metabolism in the etiology and clinical course of cannabinoid addiction represent a promising direction for future work.

Glutamate transporter 1 (GLT-1) expression is downregulated in the nucleus accumbens of chronically exposed, alcohol-preferring rats (Das et al. 2015), in

contrast to a lack of modulation in intermittently exposed animals (Griffin et al. 2015; Madayag et al. 2017; Pati et al. 2016), suggesting that perturbation of the glutamate-glutamine cycle may be involved in the formation of alcohol addiction. This hypothesis is borne out by extensive experimentation that shows reduction in alcohol preference and consumption that can be elicited by administration of compounds, for example, ceftriaxone (a β-lactam antibiotic), which upregulate GLT-1 (Alasmari et al. 2016; Das et al. 2015; Sari et al. 2016). Additional evidence comes from experiments with designer receptors activated by designer drugs (DREADD), where stimulation of glutamate release in astrocytes of the core of the nucleus accumbens was sufficient to inhibit ethanol self-administration (Bull et al. 2014). On the whole, the findings concerning glutamate transport in the opiate abuse disorder models to date echo the results from alcohol abuse investigations.

It has been established that morphine reduces expression of GLT-1 in astrocytes in culture through its activation of protein kinase C (Wang et al. 2017), and similar results have been obtained in the murine cerebrum (Wu et al. 2008). However, the effect seen in animals is sex-specific, being limited to male mice. Illuminating results were obtained in the study of heroin self-administration and withdrawal in rats (Shen et al. 2014), where heroin-seeking behavior was found to be dependent on glutamate accumulation in the core compartment of the nucleus accumbens. The "spillover" could be linked to GLT-1 downregulation, while the attenuation of the heroin-seeking behavior by ceftriaxone was mediated by GLT-1 re-synthesis. Interestingly, the specific light chain of cystine-glutamate exchanger (xCT) becomes overexpressed under the extinction conditions. This complexity underscores the importance of further inquiry into how the varied and parallel energy metabolism fluxes involving astrocytes may be involved in substance abuse disorders.

Of the numerous brain regions studied, none exhibited any alteration of GLT-1 expression associated with amphetamine exposure in rats (Sidiropoulou et al. 2001). Effects of methamphetamine, in comparison, depend on the exact behavioral model but include upregulation of GLT-1 in the striatum and medial prefrontal cortex (Han et al. 2014; Shirai et al. 1996). Change of xCT expression is documented with short-term amphetamine administration, where a reduction in the thalamus and frontal cortex is observed (Pang et al. 2013). Thus, regulation of xCT that is seen with the amphetamines resembles the one in the models of opiate abuse in that it is reciprocal with the direction of any effects on GLT-1.

In cocaine use disorder models, both GLT-1 (Knackstedt et al. 2010; LaCrosse et al. 2016; Reissner et al. 2014; Reissner et al. 2015; Sondheimer and Knackstedt 2011) and xCT (LaCrosse et al. 2017; Sondheimer and Knackstedt 2011; Trantham-Davidson et al. 2012) are found to be downregulated in the nucleus accumbens, but not in the dorsal striatum or prefrontal cortex (Knackstedt et al. 2010; LaCrosse et al. 2016; Parikh et al. 2014; Reissner et al. 2014). Both changes, and the attendant impairment of glutamate turnover, have been linked to cocaine-seeking behavior. Interestingly, the GLT-1 downregulation is progressive with the length of cocaine administration as well as the length of the abstinence period (Fischer-Smith et al. 2012). The main features of glutamate transport dysregulation triggered by cocaine use, therefore, contrast with the pattern seen in the other reviewed substance abuse

models: xCT and GLT-1 transport systems appear to be engaged in parallel pathways that drive the dependence behavior. Arriving at a unified concept of glutamate turnover dysregulation and the likely associated energy metabolism perturbations in substance use disorders will require a quantitative systems approach.

Genetic Models

Recent work has begun to address the role of metabolism and glial cells in animal models of major psychiatric disorders that incorporate genetic disruptions known to be associated with these diseases. Significant advances have been made, in particular, using the *DISC1* (disrupted in schizophrenia 1) model. Mutations in the *DISC1* gene are a rare but highly penetrant risk factor. The gene was originally identified as affected in a familial chromosomal translocation. In addition to schizophrenia, it is associated with major depression and bipolar disorder (Brandon and Sawa 2011; Millar et al. 2000; St Clair et al. 1990). The balanced (1:11) (q42.1; q14.3) translocation segregated with conditions that included schizophrenia, bipolar syndrome, and depression, in the affected family (Millar et al. 2001). Remarkably, *DISC1* was not found among the large number of loci linked to schizophrenia in a multistage genome-wide association study (Schizophrenia Working Group of the Psychiatric Genomics 2014). The totality of these data, therefore, suggests that *DISC1* may be a general psychiatric risk factor. Accordingly, mechanistic investigations of this factor could shed light on the pathophysiology of more than one condition (Farrell et al. 2015).

The translocation-related disruption results in truncated transcripts of the gene, and expression of various truncated forms of DISC1 can perturb cellular functions and brain development (Brandon and Sawa 2011; Kamiya et al. 2005). Animals expressing mutated DISC1 show behavioral phenotypes that can serve as models of schizophrenia, depression, and other major mental diseases (e.g., Abazyan et al. 2010; Abazyan et al. 2014; Ayhan et al. 2011; Clapcote et al. 2007; Lipina et al. 2013; Pletnikov et al. 2008; Shen et al. 2008; Sultana and Lee 2020). The study of the mechanisms underlying these abnormalities has highlighted a number of processes that are affected by DISC1 disruption in neurons (see, e.g., Pletnikov et al. 2007; Pletnikov et al. 2008; Jaaro-Peled et al. 2009; Brandon and Sawa 2011; Ramsey et al. 2011; Ayhan et al. 2011; Holley et al. 2013; Kim et al. 2015a; Shevelkin et al. 2017). The gene, however, is also expressed in glial cells including oligodendrocytes and astrocytes and can alter their development if disrupted (Hattori et al. 2014; Katsel et al. 2011b; Katsel et al. 2018; Kuroda et al. 2011; Seshadri et al. 2010). In addition, expression of mutant DISC1 in astrocytes can affect neuronal development, with associated behavioral effects (Terrillion et al. 2017). Thus, it is becoming clear that among the functions regulated by this pleiotropic gene, the ones mediated by its expression in astrocytes may be at the crossroads of pathways leading to major mental disease.

Recent work has begun to uncover the connections between the molecular role of the DISC1 risk factor and the role of the astrocyte energy metabolism in mental illness. Localization of *DISC1* products to mitochondria and their involvement in such functions as mitochondria trafficking and mitochondrial ATP production, oxidative phosphorylation, and calcium buffering were uncovered in the course of characterization of this gene in neurons and neuronal models (Eykelenboom et al. 2012; James et al. 2004; Ji et al. 2014; Millar et al. 2005; Norkett et al. 2016; Ogawa et al. 2014; Pinero-Martos et al. 2016), while proteomic data pinpointed involvement of DISC1 in regulation of expression of mitochondrial glucose-3-phosphate dehydrogenase in astrocytes (Xia et al. 2016). Importantly for the progress made in deciphering *DISC1* functions, astrocyte-specific expression of mutant DISC1 has the capacity to downregulate the endogenous wild-type gene in this cell type (Ma et al. 2013). The experiments also provided evidence that DISC1 binds serine racemase, while the mutant protein lacks this interaction, causing ubiquitin-mediated degradation of serine racemase in astrocytes. This is accompanied by behavioral changes characteristic of the NMDAR hypofunction models of mental disease, which could be explained by the well-documented role of D-serine as a co-ligand of NMDAR and astrocytes being its major source (e.g., Mothet et al. 2000; Panatier et al. 2006). Furthermore, when expressed in cultured astrocytes, a dominant-negative human variant of DISC1 suppresses the levels of glucose transporter 4; the same outcome can be obtained by knocking down the gene in mouse astrocytes (Jouroukhin et al. 2018). The induced changes lead to a pronounced inhibition of glucose uptake into the cells, as well as of glycolysis and oxidative phosphorylation. Both basal and maximal respiration are reduced, along with lactate production. The latter effect is not mediated by any downregulation of monocarboxylate transporter 4, indicating a purely intracellular metabolic-flux effect. The data point to downregulation of a series of steps in the glucose catabolism pathways, and a similar reduction of the lactate content could be observed in the hippocampus. In vivo, the effect on lactate is not accompanied by any change in the blood lactate concentration, supporting the notion of a local, astrocyte-dependent regulation by the dominant-negative DISC1. Strikingly, the behavioral alterations documented for astrocyte-restricted dominant negative DISC1 expression (Terrillion et al. 2017) can be rescued by administration of lactate to the mice (Jouroukhin et al. 2018). The results strongly suggest that DISC1 alters the energy metabolism in astrocytes to affect metabolite exchange with neurons, triggering the behavioral changes associated with mental disease etiology.

The implications of these findings for the role of the astrocyte energy metabolism are supported by our most recent study (Shevelkin et al. 2020). We showed that trace fear conditioning is impaired by downregulation of DISC1 in hippocampus, while no effect is observed in animals with an astrocyte-specific knockdown in the prefrontal cortex. Both spatial density of astrocytes and morphology of their protrusions are perturbed by the knockdown, as remarkably are the expression and localization of numerous proteins associated with energy metabolism. We demonstrated that pyruvate dehydrogenase and translocase of the mitochondrial inner membrane exhibit a more localized distribution in the knockdown mice. These results are

consistent with DISC1 belonging to the mammalian mitochondrial contact site and cristae organizing system and being essential for the processes of oxidative phosphorylation (Park et al. 2010; Pinero-Martos et al. 2016). Additionally, GLAST becomes positioned closer to several mitochondrial markers (Shevelkin et al. 2020), which is suggestive in light of other recent findings (Jackson et al. 2014) that showed that GLAST proximity to mitochondria regulates glutamate uptake. Furthermore, nonapoptotic caspase 3 activation was detected in neurons within the territories of affected astrocytes, and these changes were associated with perturbed glutamatergic and GABAergic markers. Thus, in addition to arguing in favor of the notion that astrocyte energy metabolism is crucial to the etiology of major psychiatric disorders, these findings suggest specific new mechanisms of astrocyte-neuron cooperation, whose perturbations may underlie development of schizophrenia and other mental illnesses. At the same time, the picture remains far from complete, and new work will be required to fill such obvious gaps as the potential role of mitochondria redistribution in the cell, which may impact the metabolic flux locally without gross changes of enzyme expression. Another topic that deserves attention is how the regulation of the overall energy flux may be affected by intracellular calcium dynamics, which is likely to act in a feedback or feed-forward manner, being modulated by the state of polarization of the mitochondrial membrane while controlling both glucose and oxygen supply.

The involvement of DISC1 in neurobehavioral abnormalities observed in substance use disorder models is starting to provide additional clues about the mechanism of its action in the affected brain. In connection with the involvement of the serine oxidation metabolism in the nucleus accumbens (reviewed in the previous subsection), it is remarkable that self-administration of cocaine in the rat model upregulates expression of DISC1 in this brain region (Gancarz et al. 2016). This finding is especially suggestive when juxtaposed with the long-known accumulation of a nuclear isoform of DISC1 in the orbitofrontal cortex of patients suffering not only from schizophrenia or major depression but also from substance abuse (Sawamura et al. 2005). Conversely, mutant DISC1 expression attenuates methamphetamine-induced behavioral sensitization in mice (Pogorelov et al. 2012) while mimicking and potentiating the cannabinoid receptor 1 downregulating effect of tetrahydrocannabinol treatment (Ballinger et al. 2015). Collectively, these findings open the possibility of involvement of the astrocyte metabolism in the molecular factors contributing to the etiology of a spectrum of substance use disorders, given the intersection of serine and energy metabolism. It is also hypothetically possible that the perturbations of glycogen synthase kinase 3β activity in the nucleus accumbens, which has been detected in the cited studies, have more direct implications for astrocyte energy metabolism. Additional work is needed to probe the potential connections between expression of the DISC1 forms, metabolism, and the mechanisms driving substance abuse, as well as any generalizations between them and the findings that have recently implicated the DISC1 risk factor in the astrocyte energy metabolism contribution to other major psychiatric disorders.

Less is known, by comparison, about the role played by metabolic alterations in other genetic models. However, the recent data are indicative of their possible

involvement and should motivate further targeted investigation of these questions. So, for example, knockout of STOP, a microtubule-stabilizing protein known for its involvement in glutamate turnover and association with cognitive defects, is accompanied by well-defined metabolic changes (Hanaya et al. 2008; Volle et al. 2013). While glucose utilization in this model is increased in the olfactory cortex, ventromedial and anterolateral hypothalamus, ventral tegmental area, and substantia nigra pars compacta, both total glutamine and glutamine derived from the preferred astrocyte substrate, acetate, are decreased (Brenner et al. 2007). These findings are strongly suggestive of involvement of astrocyte metabolism in hyperdopaminergia characterizing this mouse model and its attendant major behavioral changes. Further work is needed to clarify this apparent relationship. This need is only more urgent in light of the recent demonstration of sleep-wake cycle disruptions in the STOP model, which correlate with those seen in schizophrenia patients (Pocivavsek and Rowland 2018; Profitt et al. 2016).

Recent results concerning the neuregulin 1 model (Buonanno 2010; Law et al. 2004; Shi and Bergson 2020; Skirzewski et al. 2020) similarly raise the possibility that astrocyte energy metabolism may be involved. Indeed, neuregulin family ligands, including neuregulin 1, are potent modulators of glucose and lipid metabolism in various tissues (see Zhang et al. 2018). Although the best-studied molecular mechanism in the neuregulin 1 model of schizophrenia is the neuronal plasticity pathway, it can be noted that astrocytes express both neuregulin 1 and its receptors, including ErB4 receptor widely implicated in metabolic regulation in other tissues (Kronenberg et al. 2019; Lacroix-Fralish et al. 2006). Elucidation of the metabolic impact of neuregulin signaling in astrocytes, and its connection to the characteristic symptoms modeled by neuregulin 1 insufficiency, can represent a promising direction of research.

An additional line of investigation may be suggested by findings related to the reelin (*Reln*) model of schizophrenia (Sawahata et al. 2020; Sobue et al. 2018). In connection with this model, it is of interest that region- and layer-specific, bidirectional alteration of cytochrome oxidase activity has been observed in the brain of *reeler* (*Reln*$^{-/-}$) mice (Hayzoun et al. 2007; Lalonde et al. 2004; Strazielle et al. 2006). Supporting this picture, similar results have been reported in mice mutant for disabled-1 (DAB1) protein, a downstream partner of *Reln* (Jacquelin et al. 2013). The possibility that some of these changes are mediated by metabolic effects in astroglia appears plausible, given the recently documented expression of reelin in astrocytes (Zeisel et al. 2018) and fine but specific morphological alterations displayed by astrocytes of *reeler* mice (Lanjakornsiripan et al. 2018). Whether astrocyte energy metabolism is a contributing factor to the behavioral abnormalities of the *reeler* phenotype remains to be determined.

Therapeutic Possibilities

While it is probably correct to characterize the current state of developing treatments that would target astrocyte energy metabolism as nascent, at least two therapeutic avenues are being pursued. We have noted that obesity and the metabolic syndrome are frequent comorbidities with neuropsychiatric conditions. In this regard, a regimen of ketogenic diet or exogenous ketone supplementation to alleviate the symptoms of schizophrenia and other major psychiatric disorders is a noteworthy effort (Kovacs et al. 2019; Sarnyai and Palmer 2020). Ketone bodies are produced by the liver and in the brain also by astrocytes (Guzman and Blazquez 2004; Le Foll and Levin 2016). In addition to this direct involvement in ketogenesis, astrocytes' metabolism is changed in response to ketosis, as demonstrated by the finding that β-hydroxybutyrate downregulates the expression of both astrocytic GABA transporter GAT-1 and GABA transaminase, which can lead to an increased GABA concentration in the brain (Suzuki et al. 2009). Interestingly, another study found that in addition to GABA, the turnover of glutamate and glutamine, as well as aspartate in astrocytes, was increased in rats on a ketogenic diet (Melo et al. 2006). Astrocyte morphology is also significantly altered (Gzielo et al. 2019). Demonstration of clinical efficacy has been limited to an uncontrolled study and a number of individual cases, which, perhaps tellingly, include a complete remission of severe schizophrenia accompanied by reversal of severe obesity (Sarnyai et al. 2019; Sarnyai and Palmer 2020). The promise of these cases is supported by reversal of behavioral deficits in the MK-801 mouse model after 3 weeks of ketogenic diet (Kraeuter et al. 2019). A broadly analogous picture is presented by the existing experience with ketogenic diet in autism spectrum disorder patients (Evangeliou et al. 2003; Gogou and Kolios 2018; Spilioti et al. 2013) and rodent models (Ahn et al. 2014; Castro et al. 2017; Ruskin et al. 2013; Ruskin et al. 2017; Verpeut et al. 2016), where it can reduce stereotypic behavior and improve sociability. Evidence is growing that depression may respond to ketogenic diet similarly (Brietzke et al. 2018; Sussman et al. 2015), while limited data concerning bipolar disorder are mixed (Bostock et al. 2017). Additional studies are clearly warranted that would clarify the benefits of a tailored diet regimen and the role played by the astrocyte energy metabolism in any beneficial effects.

A promising medication-based direction utilizing the insights into brain metabolism to counter neuropsychiatric symptoms involves the use of pioglitazone and related thiazolidinedione compounds. Although pioglitazone is known as an agonist of peroxisome proliferator-activated receptor γ (PPARγ), there is pharmacological evidence that its mechanism of action, and that of the closely related compounds, in brain metabolism may not be mediated by PPAR (Dello Russo et al. 2003). The effect of pioglitazone on astrocytes involves cAMP and protein kinase A and comprises hyperpolarization of mitochondria as well as an increased glucose uptake through GLUT1 in the absence of this transporter's overexpression. Recent studies have found pioglitazone effective as adjuvant therapy with regard to negative symptoms in schizophrenia (Cakici et al. 2019; Iranpour et al. 2016). Detailed evaluation

showed that depression, but not cognitive score, could be improved, along with organism-level metabolic parameters such as blood glucose in patients with the common comorbidity affecting this parameter (Smith et al. 2013). Consistent with these results, pioglitazone and another PPARγ agonist, rosiglitazone, were found effective in a number of trials involving patients with major depression (Colle et al. 2017; Kashani et al. 2013; Kemp et al. 2012). Furthermore, depressive and anxiety symptoms in patients with bipolar disorder who exhibited treatment-resistant depression in addition to metabolic syndrome could be relieved by adjunctive administration of pioglitazone (Kemp et al. 2014). However, the results of pioglitazone treatment in cohorts not exhibiting or not selected for the presence of metabolic syndrome—a frequent co-morbidity—have been mixed (Aftab et al. 2019; Zeinoddini et al. 2015). Also, irritability, stereotypical behavior, and hyperactivity symptoms were improved in studies that tested pioglitazone in children with autism (Boris et al. 2007; Ghaleiha et al. 2015), although it is possible that these effects are mediated by anti-inflammatory action of the thiazolidinediones (Hafizi et al. 2019). Collectively, these clinical findings have led to the current concept that PPAR agonists hold out great promise in treatment of a number of neuropsychiatric disorders (Tufano and Pinna 2020). In addition to representing an application of the studies of astrocyte metabolism to the clinic, future work on PPAR agonist-based therapy may yield further insight into the role of energy metabolism in determining the clinical course of these psychiatric conditions.

Outlook

The study of the role played by the astrocyte energy metabolism in etiology of major psychiatric conditions is experiencing an acceleration brought about by accumulation of a critical mass of results. The pathways of neuron-astrocyte metabolic cooperation are being disentangled with the use of new research technologies, and the place of the astrocytes in metabolic signaling to and from the brain is being assessed. Among the outstanding fundamental questions is not only the clarification of the intensity but also the directionality of metabolite exchange in the brain tissue under the conditions of upregulated metabolism in sustained cognitive tasks and how their disruption accompanies cognitive abnormalities characteristic of mental disease. It will be necessary to more fully integrate our understanding of genetic risk factors in major psychiatric disorders with the picture being painted by metabolomic and functional assessment of the affected brain and individual cell types, particularly glia and astrocytes. Animal models and in vitro research have the potential to uncover the missing links between genotype and the pathological behavioral phenotype. As these studies are beginning to indicate promising avenues for therapeutic treatment of the most severe symptoms, much more work is needed to arrive at a system-level understanding of the energy metabolic processes that implicate astrocytes in major mental disorders.

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Part IV
Astroglia in Addictive Disorders

Astrocytes in Addictive Disorders

Anna Kruyer and Michael D. Scofield

Overview of Addiction Biology

Circuitry and Transmitters

The elevation of extracellular dopamine in the ventral striatum in response to salient and rewarding stimuli underlies several reinforcement and addiction-related behaviors extensively studied in preclinical models of substance use and relapse (Scofield et al. 2016a). Anatomically, the ventral striatum is divided into two subregions, the nucleus accumbens core (NAcore) and shell (NAshell), which both receive dopaminergic innervation from the midbrain nucleus the ventral tegmental area (VTA) (Ikemoto 2007) and that are both involved in encoding reward and motivation. Increased levels of extracellular dopamine in the ventral striatum are evoked by administration of addictive drugs (reviewed in (Willuhn et al. 2010)) including alcohol (Howard et al. 2008), as well as by sucrose intake (Bassareo et al. 2017), and a substantial body of lesion, microdialysis, voltammetry, and pharmacology studies has led to the general conception that the NAshell is involved in encoding the rewarding effects of addictive drugs, while the NAcore coordinates behavioral outputs in response to salient stimuli (Scofield et al. 2016a; Sellings and Clarke 2003; Salgado and Kaplitt 2015).

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Though natural (i.e., sucrose) as well as pathological (i.e., drugs of abuse) rewards elevate dopamine in the ventral striatum, dopaminergic signaling within this circuit is modulated by glutamatergic transmission, and glutamatergic signaling is uniquely disrupted following repeated intake of addictive substances (Kalivas et al. 1989, 2009; Kalivas 2009). In keeping with important but separable roles for these two transmitters in addiction-related behaviors are recent studies demonstrating that subpopulations of dopaminergic VTA neurons that project to the NAshell co-release glutamate along with dopamine (Stuber et al. 2010; Mongia et al. 2019; Mingote et al. 2019). Glutamate release from dopamine neurons in the NAshell is linked to intake of sucrose and psychostimulants and locomotor responses to acute and repeated psychostimulant administration (Hnasko et al. 2010; Alsio et al. 2011; Birgner et al. 2010; Bimpisidis and Wallen-Mackenzie 2019). Glutamate modulates dopamine neurotransmission through its action on glutamate receptors expressed on dopaminergic terminals (Floresco et al. 1998; Howland et al. 2002) and through facilitation of dopamine loading in synaptic vesicles (Hnasko et al. 2010; Hnasko and Edwards 2012). Though VTA inputs to the NAcore contribute to drug seeking induced by drug prime (Shen et al. 2014a), the impact of dopamine transmission on seeking behavior can be blocked by glutamate receptor antagonists even in the presence of dopamine (Cornish and Kalivas 2000), consistent with a critical role for glutamatergic transmission in drug seeking behavior.

The ventral striatum receives excitatory input from a number of brain regions, in addition to VTA. Cortical regions provide glutamatergic input to the NAcore and NAshell, with prelimbic (PL) cortical afferents in the NAcore or infralimbic (IL) afferents in the NAshell contributing to drug seeking or refraining behavior, respectively. Glutamate transmission in the NAcore is necessary for initial learning of drug-reward associations (Kelley et al. 1997; Smith-Roe and Kelley 2000) and later for retrieval of drug-contingency information during reinstatement of drug seeking following extinction of behavioral responding (Kalivas 2009; Kalivas and Volkow 2005; Koob and Volkow 2010). PL afferents in the NAcore are engaged during cue-, drug-, context- and stress-reinstated seeking of different classes of addictive substances, including opioids, psychostimulants, and alcohol (Rogers et al. 2008; Ball and Slane 2012; Rocha and Kalivas 2010; Doncheck et al. 2020; McFarland et al. 2003; Willcocks and McNally 2013; Chaudhri et al. 2008). The IL input to the NAshell, on the other hand, is recruited during extinction training, whereby operant responding for drug reinforcers is gradually reduced over time when the drug is no longer available (Peters et al. 2008).

The NAcore also receives significant glutamatergic input from basolateral amygdala (BLA) that contributes to both acquisition of self-administration and reinstatement initiated by cues (Carelli et al. 2003; Whitelaw et al. 1996; Di Ciano and Everitt 2004; Puaud et al. 2020), through direct glutamatergic projections to the NAcore and/or projections to the PL (Stefanik and Kalivas 2013). BLA glutamate may also be engaged to a certain extent by operant training for natural reinforcers, since optogenetically stimulating BLA projections to the NAcore can initiate responding for sucrose (Stuber et al. 2011). A number of other brain regions have been strongly implicated in promoting addiction-related behaviors, including dorsal

and ventral hippocampus (Fuchs et al. 2005; Lasseter et al. 2010; Atkins et al. 2008), ventral subiculum (Bossert and Stern 2014), and lateral septum (McGlinchey and Aston-Jones 2018), though not necessarily via direct NAcore projections. Interestingly, excitatory projections to the NAcore can also suppress seeking behavior, since glutamate release from the paraventricular thalamus in the NAcore serves to suppress seeking behavior in the absence of a reinforcer (Do-Monte et al. 2017), arguing that excitatory transmission in the NAcore is necessary, but not sufficient for reward seeking, and that unique innervation of postsynaptic targets may be an important factor in ultimate behavioral outputs.

Astrocytes are likely mediators of the long-lasting excitatory plasticity that arises within the corticostriatal circuitry in response to chronic drug intake. Astroglial processes are positioned proximal to excitatory synapses, and their expression of neurotransmitter transporters regulates stimulation of pre- and postsynaptic receptors. Moreover, astroglia are capable of signaling directly to synapses through transmitter release and play critical roles in homeostatic regulation of synapses. Astroglial adaptations following exposure to addictive drugs are being actively investigated within the circuits outlined above. Given that vast brain region-dependent heterogeneity in astroglial structure and transcriptomic profiles has recently been described (Batiuk et al. 2020; Matias et al. 2019; Cuevas-Diaz Duran et al. 2019; Kohler et al. 2019), astrocyte function as it pertains to addiction is likely unique in each region. Below we explore what is known regarding astroglial contributions to synaptic physiology at baseline and after use of addictive substances.

Transmitter Uptake

Glutamate

The glutamate transporter GLT-1 (EAAT2 in humans) conducts the majority of glutamate uptake and is mostly expressed by astroglia in the adult brain (Danbolt 2001), despite reports of low-level expression in some neurons (Rimmele and Rosenberg 2016). GLT-1 has long been thought to contribute to addiction-related glutamatergic dysregulation in the ventral striatum since its expression and/or function is disrupted after long-term use of psychostimulants, opioids, and alcohol (Roberts-Wolfe and Kalivas 2015). GLT-1 knockdown in astroglia during the early postnatal period leads to repetitive behaviors in drug-naïve animals and enhanced neuronal excitability in the dorsal striatum (Aida et al. 2015). In rats trained to self-administer cocaine, GLT-1 downregulation in the NAcore is dependent upon withdrawal duration as well as cocaine intake, with increasing amounts of either exacerbating the severity of GLT-1 downregulation (Fischer-Smith et al. 2012). Further, extended withdrawal from long-access cocaine self-administration (i.e., daily 6-hour sessions) reduces mRNA levels of the predominant of three GLT-1 isoforms, GLT-1a (Holmseth et al. 2009), in the NAcore, coincident with enhanced

methylation of *Slc1a2*, the gene that encodes GLT-1 (Kim et al. 2018). Since the authors of this study found no changes in GLT-1a or b mRNA levels after withdrawal or extinction from short access cocaine self-administration, but many other studies show GLT-1 downregulation in these paradigms (Roberts-Wolfe and Kalivas 2015), it may be that posttranslational rather than transcriptional mechanisms are responsible for its reduced expression and/or function in short-access models. Interestingly, up- or downregulation of GLT-1 in the striatum disrupts spike-timing dependent plasticity, a type of long-term potentiation that requires a tight temporal relationship between pre- and postsynaptic activity (Valtcheva and Venance 2016). When the action of GLT-1 is blocked, long-term potentiation requires signaling through extrasynaptic GluN2B-containing NMDA receptors. Similarly, signaling through GluN2B is required for cue- or heroin prime-induced reinstatement of heroin seeking (Shen et al. 2011). These data are consistent with diminished function of GLT-1 after extinction from heroin self-administration (Shen et al. 2014b). Further, disrupted forms of synaptic plasticity involving downregulated GLT-1 after drug use and/or withdrawal may conceivably impair mechanisms required for extinction learning, which is somewhat impaired in drug-trained compared with sucrose-trained animals (Martin-Fardon and Weiss 2017). Notably, operant sucrose training does not produce downregulation of GLT-1 (Kruyer and Kalivas 2020a), which may account for these behavioral differences.

A significant body of work has established that compounds that restore GLT-1 expression reduce drug craving and relapse, both in animal models and in human clinical trials (Roberts-Wolfe and Kalivas 2015). For example, the antioxidant N-acetylcysteine, the ß-lactam antibiotic ceftriaxone, and the xanthine derivative propentofylline have all demonstrated promise in restoring GLT-1 expression after drug withdrawal and in blunting reinstated drug seeking in preclinical models (summarized in (Scofield et al. 2016a)). N-acetylcysteine is extremely safe for use in humans but has proven only marginally efficacious in reducing craving and drug use in patients (summarized in (Roberts-Wolfe and Kalivas 2015)), potentially due to limited bioavailability. Given that recent studies indicate that GLT-1 upregulation alone is not sufficient to blunt reinstated cocaine seeking (Logan et al. 2018), it may very well be that additional manipulations are required to adequately suppress relapse vulnerability. Moreover, it may be the case that upregulation rather than homeostatic restoration of GLT-1 expression may not entirely restore mechanisms of synaptic plasticity, as both GLT-1 blockade and overexpression do not properly permit spike timing-dependent plasticity at striatal synapses (Valtcheva and Venance 2016).

Although drug-induced changes in GLT-1 expression after chronic use of addictive drugs have been less well documented in the midbrain when compared to the ventral striatum, astroglial glutamate transporters in the VTA also play an important role in modulating avoidance behaviors (Gomez et al. 2019). As mentioned above, the VTA sends dopaminergic, glutamatergic, as well as GABAergic projections to the nucleus accumbens, and these projections encode the reinforcing and aversive aspects of drug use (Morales and Margolis 2017). Additionally, GABAergic interneurons within the VTA regulate dopaminergic projection neurons that signal

avoidance vs. motivated approach behaviors (McCullough et al. 1993; Tan et al. 2012). This was demonstrated with optogenetic stimulation of VTA astrocytes, which permits excitation of GABAergic interneurons that inhibit dopaminergic projections and promote avoidance behavior (Gomez et al. 2019). It was subsequently shown that astrocyte-dependent facilitation of GABAergic activation depends on GLT-1, as conditional knockout of GLT-1 in VTA astrocytes impairs the optogenetic stimulation-mediated GABAergic excitation (Gomez et al. 2019). While the authors do not clarify the mechanism by which GLT-1 contributes to GABAergic excitation, they illustrate that manipulation of astroglial GLT-1 interferes with conditioned place avoidance, but does not impact conditioned place preference (Gomez et al. 2019), suggesting divergence of these circuits and a contribution of astrocytes through GLT-1 to avoidance, but not approach behavior (Gomez et al. 2019). Although changes in GLT-1 expression have not been as clearly demonstrated in the VTA after drug use and withdrawal compared with the NAcore (Knackstedt et al. 2009), analysis of GLT-1 function may be warranted given these surprising findings. These data also highlight the importance of analyzing transporter function in a pathway-specific manner, rather than in whole tissue, since functional changes that impact discrete subcircuits may not be discernable when protein levels are assessed in tissue extracts.

GABA

While uptake of glutamate release from cortical terminals in the striatum is thought to directly regulate relapse-like behaviors in animal models (Kalivas 2008), cortical stimulation triggers uptake of both GABA and glutamate by striatal astrocytes and clearance of both transmitters contributes to postsynaptic excitation of MSNs (Goubard et al. 2011). These findings illustrate the relevance of local GABAergic signaling on corticostriatal synaptic transmission and the contribution of transporter uptake in regulating striatal outputs. In support of this concept, studies where Ca^{2+} signaling in astrocytes is inhibited in vivo through viral delivery of a genetically encoded plasma membrane Ca^{2+} pump that expels cytosolic Ca^{2+} from astrocytes (CalEx) (Yu et al. 2018) demonstrate the behavioral involvement of GABA transporters expressed on striatal astrocytes in compulsive-like behaviors. Importantly, the CalEx vector reduces astroglial intracellular Ca^{2+} levels at baseline and also reduces the amplitude and duration of Ca^{2+} elevations. When delivered to astroglia in the dorsolateral striatum, CalEx expression results in upregulation of the largely astroglial GABA transporter GAT-3 and produces excessive self-grooming behavior, reminiscent of features of obsessive-compulsive disorder (Yu et al. 2018). Further, GAT-3 upregulation reduces tonic inhibition, a known role for GAT-3 that is expressed most densely in extrasynaptic zones (Melone et al. 2015), selectively at D1 receptor expressing MSNs (D1-MSNs) (Yu et al. 2018). Interestingly, when a different strategy was used to upregulate astroglial GAT-3 in a pathway-nonspecific manner, the authors found no impact on grooming behavior, suggesting that perhaps

the cell selectivity of the effects were necessary for the disrupted behavior observed by the authors.

The dorsal striatum is involved in habit learning (Yin et al. 2004) and is uniquely recruited in cases of substance use disorder characterized by compulsive seeking. For example, in humans who drink socially, but not compulsively, alcohol-associated cues stimulate activation of the ventral striatum. Instead, the same cues stimulate activation of the dorsal rather than the ventral striatum in heavy drinkers, and ventral striatal activity in response to alcohol-associated cues is negatively associated with measures of compulsive craving in these individuals (Vollstadt-Klein et al. 2010). Interestingly, compounds effective in suppressing compulsive behaviors, like N-acetylcysteine, which reduces symptoms of trichotillomania (Farhat et al. 2020) and pathological gambling (Grant et al. 2007), also reduce reinstated drug seeking in animal models (Kalivas and Kalivas 2016). As mentioned above, N-acetylcysteine was most studied in the context of addiction for its ability to upregulate GLT-1 in the ventral striatum, but its impact on astroglial expression of GABA transporters like GAT-3 in the ventral or dorsal striatum has not been assessed.

Dopamine

Although there is in vitro evidence that astrocytes can recover extracellular dopamine through expression of the dopamine transporter (DAT), norepinephrine transporter (NET), and/or plasma membrane monoamine transporter (PMAT) (Pelton 2nd et al. 1981; Takeda et al. 2002; Naganuma et al. 2014), evidence is less clear-cut in vivo. The organic cation transporter 3 (OCT3), a low-affinity monoamine transporter, has been reported on neurons and astroglia in the rodent substantia nigra and striatum (Cui et al. 2009), and electron microscopy studies revealed OCT3 on the plasma membrane of perisynaptic astroglial processes in the rodent amygdala, consistent with its role in monoamine uptake near synaptic sites (Gasser et al. 2017). OCT3 was recently found to function in reverse in the presence of amphetamine, releasing dopamine into the extracellular space (Mayer et al. 2018). The authors also confirmed that while OCT3 was expressed by dopaminergic neurons, the majority of OCT3-expressing cells were likely glia as well as non-dopaminergic neurons (Mayer et al. 2018). Importantly, while astroglia express OCT3 and therefore may also theoretically employ this mechanism, releasing dopamine in the presence of amphetamine, amphetamine enters into dopaminergic neurons through DAT and not through OCT3 (Mayer et al. 2018). Thus, in the absence of a mechanism for amphetamine uptake by astroglia, astroglial OCT3 is not likely to be involved in this process. Because studies on the contribution of OCT3 to dopamine transport in the striatum and elsewhere have emerged relatively recently (Holleran et al. 2020), there are no studies investigating changes in OCT3 expression in astrocytes following drug use and withdrawal in brain regions that contribute to addiction-related behaviors, though it remains a fundamental research question.

Gliotransmission

Glutamate

Gliotransmission by astrocytes is most often described as involving intracellular Ca^{2+} flux and vesicular exocytosis of transmitters, which signal to nearby neurons (Parpura et al. 1994; Araque et al. 2014; Papouin et al. 2017; Scofield 2018). Though electron microscopy and expression studies support the existence of vesicular release machinery in astrocytes, the relevance of this modality for gliotransmission has been contested by studies indicating a lack of glutamate receptor expression in astrocytes in the adult brain in vivo (Sun et al. 2013) as well as studies where deletion of key mediators of intracellular Ca^{2+} flux in astrocytes had little impact on neuronal function (Petravicz et al. 2014; Bazargani and Attwell 2016). Despite this, there are a number of well-established mechanisms by which astroglia signal to neurons through non-exocytotic mechanisms and without associated changes in intracellular Ca^{2+} (Agulhon et al. 2010; Gomez-Gonzalo et al. 2018). Here we will discuss evidence for exocytotic and non-exocytotic mechanisms of transmitter release given the important role for excitatory signaling in formation of drug-cue associations and in reinstatement of drug seeking.

Perhaps the least controversial mechanism for glutamate transmission by astroglia is through the cystine-glutamate antiporter, system xc-, which contributes to 60% of extracellular glutamate in the NAcore in drug-naïve animals (Baker et al. 2002). Extracellular glutamate derived from system xc- tonically stimulates presynaptic autoinhibitory mGluRs on glutamatergic and dopaminergic terminals, regulating transmitter release during neural firing (Baker et al. 2002). System xc-, which is expressed to the greatest extent by astroglia (Pow 2001; Sagara et al. 1993), is downregulated after chronic intake of psychostimulants in the NAcore, and this downregulation is thought to disrupt autoinhibitory tone at presynaptic mGluR2/3 on glutamatergic terminals, leading to enhanced glutamate release in response to drug-associated cues (Baker et al. 2002). It should be noted that system xc- is not similarly downregulated after chronic intake of opioids (Shen et al. 2014b), so this molecular adaptation may not generalize across all substances of abuse. However, the treatments described above that have been tested preclinically for their ability to attenuate reinstated seeking through restoration of GLT-1, including N-acetylcysteine and ceftriaxone, also increase expression of system xc- (Knackstedt et al. 2010), and N-aceytylcysteine may even increase extracellular cystine levels, promoting cystine-glutamate exchange. The contribution of GLT-1 and system xc- upregulation to relapse suppression has been tested by pairing these pharmacological treatments with morpholino knockdown of either GLT-1 or xCT, a subunit of system xc-, in the NAcore prior to reinstatement. In these studies, the authors found that GLT-1, not xCT, had the greatest impact on reinstated drug seeking (Reissner et al. 2015).

Studies exploring the involvement of exocytotic transmitter release by astrocytes in addiction-related behaviors has made use of transgenic mice that express a dominant negative SNARE protein (dnSNARE) in astroglia. These mice lose the

capacity to exocytose transmitter-containing vesicles through SNARE mechanisms in astroglia but retain normal mechanisms for neuronal exocytosis (Pascual et al. 2005). dnSNARE mice exhibit similar operant responding for food compared to wild-type animals but appear to take less cocaine during self-administration, despite similar rates of operant acquisition (Turner et al. 2013). dnSNARE mice also reinstate less robustly to cocaine-paired cues (Turner et al. 2013). Whether this reinstatement deficit derives in part from changes in cocaine intake is an important question, since dnSNARE animals appear to receive fewer cocaine infusions and consequently fewer cocaine-cue pairings during training. However, reinstatement of conditioned place preference (CPP) is also abolished in these mice, supporting a role for vesicular gliotransmission in reinstatement behaviors after exposure to psychostimulants (Turner et al. 2013). One limitation of these studies is that global dnSNARE expression in astroglia does not provide information regarding which brain region(s) orchestrate gliotransmission-dependent modulation of reinstatement. Interestingly, it was found that chemogenetic stimulation of Gq signaling in NAcore astrocytes, a manipulation that engages flux of internal Ca^{2+} and activates SNARE-dependent vesicular release of glutamate, reduces reinstated cocaine seeking initiated by cocaine-associated cues (Scofield et al. 2015). Similarly, astroglial Gq stimulation reduces methamphetamine (Siemsen et al. 2019) and ethanol seeking (Bull et al. 2014). It was demonstrated that the suppression of cocaine seeking using this technique was a consequence of astroglial-glutamate release that stimulated presynaptic mGluR2/3 and ultimately reduced transmitter release from presynaptic terminals (Scofield et al. 2015).

In another study, engaging Gq signaling in cultured astrocytes evoked non-vesicular glutamate release through the glutamate-permeable anion channel Bestrophin 1 (Best1) (Woo et al. 2012). Importantly, Best1 is situated near synapses in vivo and would be expected to raise extracellular glutamate levels less robustly than vesicular release. Consequently, release of glutamate through this modality is more likely to impact high-affinity NMDA receptors, compared with vesicular release which might also engage lower-affinity receptors. Accordingly, it might be expected that separate modalities of glutamate release from astrocytes engage functionally distinct intracellular signaling cascades in nearby neurons, despite both modalities being linked to Gq-coupled receptor activation. Together, the findings described above lead to important questions regarding how these cellular mechanisms are employed within the reward circuitry of drug-naïve animals and how their deployment may be impacted by chronic intake of and withdrawal from addictive substances.

One valid critique of studies where either optogenetic or chemogenetic manipulation of astrocytes is employed to understand astroglial biology is that the abundance of the exogenously expressed proteins, as well as their proximity to synapses, may not reflect normal physiological features of astroglia. Nonetheless, studies in the dorsal striatum and elsewhere clearly illustrate that astrocytes signal to local MSNs using endogenous mechanisms of glutamate release. Dorsal striatal astrocytes are uniquely tuned to respond functionally to electrical stimulation of D1- or D2-MSN subtypes in response to neuronally released endocannabinoids (eCBs), with Ca^{2+} flux and ultimately glutamate release (Martin et al. 2015). Astrocyte glutamate release produces slow inward currents (SICs) in adjacent neurons of the

same subtype as the stimulated neuron, presumably through stimulation of extrasynaptic NMDA receptors (D'Ascenzo et al. 2007), but SICs are rare in heterotypic pairs. These findings are particularly relevant given that stimulation of striatal D1-MSN projections or inhibition of D2-MSN projections trigger reinstated seeking (Heinsbroek et al. 2017; Pardo-Garcia et al. 2019). There is not yet definitive evidence for how astrocytes distinguish between neural subcircuits. It is abundantly clear that striatal astrocytes encompass both D1- and D2-MSN somata within their cellular territories (Octeau et al. 2018), so spatial segregation does not seem a likely possibility. Further, studies using dye-filling strategies illustrate that astrocytes are extensively coupled to one another through gap junctions (Octeau et al. 2018), forming large densely interconnected syncytia. Thus, it does not appear that segregated astrocyte subpopulations are joined into networks through gap junctions, at least not in drug-naïve animals (but see "Homeostatic Functions" for a discussion of drug-induced changes in astrocyte gap junctions). Still, there are a number of hypothetical ways that astrocytes might coordinate signaling within, but not between circuits, when the same receptors and transmitters are employed in both pathways. One possibility is that additional signaling molecules accompany transmitter release and astrocytes selectively express receptors for molecules released by one or the other pathway. As an example, in the ventral pallidum, D1- and D2-MSN terminals co-release unique neuropeptides, with D1-MSNs co-releasing substance P and dynorphin and D2-MSNs co-releasing enkephalin and neurotensin (Kupchik et al. 2014). The same could occur postsynaptically, with the release of different eCBs following postsynaptic excitation of either D1- or D2-MSNs or unique expression patterns of cannabinoid receptors on astroglial subtypes. Whether release of unique pre- or postsynaptic signaling molecules selectively recruits astrocytes to signal to adjacent MSNs in a homotypic manner remains to be shown. Another possibility is that astrocytes are selective in their synaptic proximity, with each astrocyte exhibiting unique proximity to D1- or D2-MSNs in order to receive and transmit signals selectively. While it does not appear that D1 or D2-MSN-containing synapses receive different degrees of astrocyte insulation overall, there is tremendous variability in synaptic insulation by astroglia in the striatum (Octeau et al. 2018; Chai et al. 2017). Thus, it remains possible that each astrocyte may exhibit some selectivity in which synapses it approaches most closely. This concept will be discussed in more depth in the subsequent section on astrocyte morphological plasticity.

D-Serine

D-serine is the R-enantiomer of the amino acid serine and functions as an NMDA receptor co-agonist, with selective affinity for the glycine binding site (Mothet et al. 2000; MacKay et al. 2019). D-serine has been studied for its improvement of positive and cognitive symptoms in schizophrenia patients when co-administered with antipsychotics (Tsai et al. 1998), based on evidence of hypofunctional NMDA receptor activity in the disorder (Coyle 2012). Whether D-serine is released by astrocytes has been a somewhat controversial topic since serine racemase, the

enzyme that converts L-serine to D-serine in cells, is mostly expressed by neurons (Yoshikawa et al. 2007; Benneyworth et al. 2012). It appears that instead, D-serine is produced by serine racemase in neurons and is shuttled between neurons and astroglia for vesicular release (Wolosker 2011; Martineau et al. 2013). Regardless of its cellular origin, D-serine has been shown to play an important role in signaling via NMDA receptors in the accumbens. D-serine is required for NMDA-dependent synaptic potentiation and depression in the NAcore (Curcio et al. 2013), both of which are disrupted after withdrawal from cocaine self-administration (Moussawi et al. 2009). Linking these findings, researchers found that cocaine reduces D-serine concentration in the NAcore through increased expression of D-amino acid oxidase, an enzyme that degrades D-serine (Curcio et al. 2013; D'Ascenzo et al. 2014). The reduction in D-serine levels increases the relative proportion of AMPA/NMDA receptors in neurons postsynaptically and permits locomotor sensitization and CPP (Curcio et al. 2013; D'Ascenzo et al. 2014; Yang et al. 2013). Subsequent studies found that morphine also decreases D-serine in the nucleus accumbens and does so by reducing surface expression of AMPA receptors on astrocytes that normally trigger Ca^{2+} flux and vesicular D-serine release (Wu et al. 2017). Despite these promising findings, additional experimentation is required to determine the precise role of D-serine gliotransmission in mediating addiction-relevant synaptic plasticity.

ATP

Astrocyte-derived adenosine has been shown to contribute to synaptic modulation in various brain regions and in response to synaptically released glutamate as well as dopamine (Pascual et al. 2005; Zhang et al. 2003; Quon et al. 2018; Corkrum et al. 2020). In the dorsolateral striatum, high-frequency stimulation of cortical terminals stimulates astroglial mGluR5, a Gq-coupled receptor, to produce Ca^{2+} increases, ATP release, and adenosine receptor-mediated long-term depression of postsynaptic cells (Cavaccini et al. 2020). In a similar study in the dorsomedial striatum, the authors show that astroglial expression of the adenosine transporter equilibrative nucleoside transporter 1, ENT1 is required for astroglial Gq stimulation to impact neural activity. Interestingly, triggering this signaling cascade alters firing properties of both D1- and D2-MSNs, reducing spontaneous EPSCs in D1- and increasing them in D2-MSNs, promoting goal-directed rather than habitual behaviors (Kang et al. 2020).

Altogether, Gq-dependent signaling in striatal astrocytes has been linked to vesicular glutamate release (Scofield et al. 2015), slow and low-volume glutamate transmission through Best1 (Woo et al. 2012), and adenosine transport through ENT1 (Kang et al. 2020), and activation of astroglial mGluR5, a Gq-coupled receptor, is linked to astrocyte release of ATP (Cavaccini et al. 2020). Perhaps it is not problematic that such a diverse range of outcomes can be recruited using the same tools or by engaging the same signaling cascade in astroglia. In most cases, it cannot be ruled out that multiple forms of gliotransmission occur following Gq receptor stimulation, as exhaustive tests are often not feasible. Also, gliotransmission in vivo

would be expected to be more refined, since local neural signals would be detected by receptors on astrocyte processes to tune local responses. Indeed, it has been demonstrated previously that the same astrocyte is capable of signaling in distinct ways using different gliotransmitters depending on the dynamics of incoming signals (Covelo and Araque 2018), supporting the tremendous plasticity of this cell type.

Synaptic Proximity

Morphological Plasticity of Astrocytes

A central aspect underlying efficacy of transporter uptake and gliotransmission is the physical proximity of astroglial processes with synapses (see Fig. 1). The fidelity of this spatial relationship is crucial for normal neurobiology since perisynaptic astroglial processes (PAPs) express machinery for uptake and release of transmitters and maintenance of homeostatic neuronal function. Interestingly, PAPs display morphological plasticity more dynamic than what is observed in dendritic spines (Haber et al. 2006), and astrocyte morphological plasticity has been reported in the presence of extracellular glutamate (Genoud et al. 2006; Bernardinelli et al. 2014a; Verbich et al. 2012; Perez-Alvarez et al. 2014) and dopamine (Galloway et al. 2018). In the hippocampus, astroglial processes exhibit enhanced physical interaction with

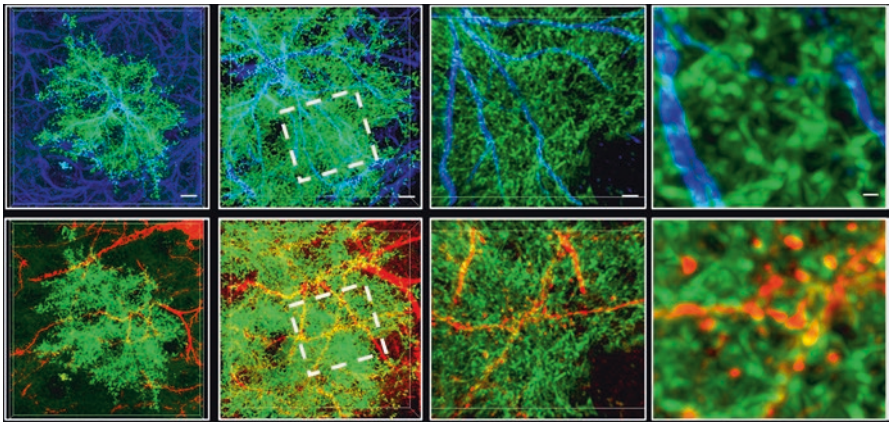

Fig. 1 Super-resolution confocal imaging of an astroglial plasma membrane, GFAP arbor and neighboring dendritic segment on an NAcore-projecting PL neuron. *Top*, plasma membrane labeling of an astrocyte in the PL using the AAV-GFAP-LcK-GFP viral vector from the Khakh laboratory (green) (Shigetomi et al. 2013). Immunohistochemical labeling of the cytoskeletal protein GFAP is shown in blue. *Bottom*, association of the astrocyte plasma membrane (green) with a retrogradely labeled dendritic segment from a neighboring PL neuron that projects to the NAcore (red). Here the neuron was labeled with retrograde delivery of Cre in the NAcore combined with Cre-dependent AAV-DIO-mCherry expression in the PL. For both the top and bottom series, panels transition to higher magnification to show detail from left to right. The dashed box depicts the inset region, scale bars are 10, 5, 2 and 0.5 microns

the postsynaptic compared with the presynaptic compartment (Lehre and Rusakov 2002). Further, astroglial interaction with neurons in this region tends to be biased toward dendritic spines as opposed to the larger dendritic shaft (Gavrilov et al. 2018). The general consensus regarding this conformation is that PAPs are positioned to perform glutamate transport upon transmitter release while also permitting a degree of transmitter spillover presynaptically, allowing for stimulation of presynaptic autoreceptors as a negative feedback loop that maintains elegant regulation of transmitter release probability.

In the striatum, there is a tremendous degree of variability in synaptic insulation by astroglial processes, perhaps due to the different input types (dopaminergic vs. glutamatergic), with astrocytes more closely abutting glutamatergic vs. dopaminergic terminals (Octeau et al. 2018). Regarding postsynaptic selectivity, high-resolution techniques have been applied to astrocytes and different synapse types in the striatum to demonstrate that astrocytes encompass similar numbers of D1- and D2-MSNs, with a slight bias toward D1-MSNs (Octeau et al. 2018). Nevertheless, both neuronal types receive similar degrees of synaptic insulation by astrocytes (Octeau et al. 2018).

Impact of Synaptic Insulation on Synapse Function

Synaptic proximity of astrocyte processes promotes synapse stability and maturation (Bernardinelli et al. 2014b; Nishida and Okabe 2007; Blanco-Suarez et al. 2018), and it is taken for granted that transmitter uptake and release by astrocytes requires a high degree of synaptic proximity to effectively regulate synaptic physiology. Not only would loss of synaptic apposition impact efficacy of these functions, but synaptic retraction of astrocyte processes has been shown to favor synaptic recruitment at excitatory synapses, with transmitter spillover potentiating nearby synapses when astrocyte processes have retracted (Henneberger et al. 2020). Retraction of astroglial processes may also permit stimulation of extrasynaptic glutamate receptors (Pal 2018; Kruyer and Kalivas 2020b) and impact neuronal excitability and plasticity. Extrasynaptic mGluRs pertinent to excitatory signaling underlying relapse include the aforementioned presynaptic mGluR2/3 that serves as a brake on glutamate and dopamine release (Xi et al. 2002) and mGluR5 expressed on nNOS interneurons that initiate degradation of the extracellular matrix and facilitate postsynaptic potentiation (Smith et al. 2017; Kruyer et al. 2019a).

Glutamate spillover permitted by retraction of astrocyte processes also recruits high-affinity NMDA receptors, which play an important role during drug relapse. The GluN2b (NR2b or NMDAR2b) subunit is largely extrasynaptic, as opposed to the mostly synaptic GluN2a (D'Ascenzo et al. 2007). Stimulation of GluN2b-containing NMDA receptors contributes to postsynaptic potentiation during reinstated heroin seeking, and GluN2b knockdown or blockade prevents increases in AMPA/NMDA and spine head diameter induced by a priming heroin injection and reduces reinstated seeking induced by cues or heroin prime (Shen et al. 2011).

Drug-Induced Morphological Plasticity

Astrocytes exhibit profound morphological adaptations after exposure to substances of abuse. For example, astrocyte volume is reduced in the NAcore by exposure to both opioids and psychostimulants (Siemsen et al. 2019; Scofield et al. 2016b; Kruyer et al. 2019b). NAcore astrocytes are also more densely packed after alcohol and astrocyte density correlate positively with breakpoint for ethanol, a measure of motivation to acquire alcohol (Bull et al. 2014). Analysis of astrocyte plasticity is complicated given that both immunological and synaptic events can impact their morphology, and substances of abuse can trigger both types of CNS adaptations. For example, chronic cocaine or morphine exposure causes reactive astrogliosis characterized by changes in GFAP expression, a type of neuroinflammation that induces an altered functional and morphological state in astroglia (Beitner-Johnson et al. 1993; Sil et al. 2018; Bowers and Kalivas 2003). Whether changes in astrocyte proximity to synapses is a by-product of an immunoreactive state and whether synaptic functions of astroglia are interrupted by immunological processes is an ongoing question that necessitates further investigation.

Recent studies show that cues that stimulate drug seeking trigger morphological plasticity in NAcore astrocytes in animals trained to self-administer heroin, but not sucrose (Kruyer et al. 2019b). This plasticity appears homeostatic in nature, resulting from cue-induced neuronal activity and glutamate release. Moreover, interrupting the re-association of astroglial processes with synapse during reinstatement elevates responding for cues that signal heroin availability. Changes in synaptic proximity of astrocyte processes in this case are linked to phosphorylation of ezrin, an actin-blinding protein selectively expressed in astroglial processes (Derouiche and Frotscher 2001). Currently, neither the signaling cascade that drives ezrin phosphorylation nor the mechanism by which astrocyte process motility suppresses reinstated seeking has been uncovered. Additionally, whether NAcore D1- or D2-MSN synapses retain different degrees of astrocyte insulation during withdrawal from drug use or during reinstated seeking is a fundamental remaining question.

Homeostatic Functions

Synaptogenesis

Astrocytes play key roles in both synapse formation and elimination. Astrocytes express and release several signaling factors that contribute to formation of dendritic spines and spine density (Walker et al. 2020; Ikeda et al. 2010; Wang et al. 2020a; Chung et al. 2015), a measure that is aberrantly altered in the striatum after drug use and during reinstated drug seeking (Shen et al. 2011; Dos Santos et al. 2017; Anderson and Self 2017). During development, thrombospondins released by astrocytes promote genesis of new synapses that are postsynaptically silent

(Christopherson et al. 2005). In adult animals, thrombospondin expression is elevated in response to cocaine exposure, and astrocyte thrombospondins in the NAshell contribute to generation of silent synapses (Wang et al. 2020b). In both cases, it is expected that presence of silent synapses facilitates induction of functional synapses rapidly upon further signaling that induces postsynaptic insertion of AMPA receptors. Indeed blocking thrombospondin release by astroglia during exposure to cocaine cues blunts cued reinstatement of seeking (Wang et al. 2020b), which is strongly linked to measures of postsynaptic potentiation (Gipson et al. 2013). Astrocytes also participate in synapse elimination, through phagocytosis directly, and through coordinated signaling with microglia (Chung et al. 2013, 2015; Wilton et al. 2019). While astrocytes prune synapses to refine neural circuits during development, there is evidence that astrocytes express the machinery for synapse engulfment into adulthood (Chung et al. 2015), and recruitment of this process during acquisition of drug taking behavior or extinction learning is a possibility.

BDNF, a growth factor expressed and released by both astrocytes and neurons (Zafra et al. 1991; Ohno et al. 2018; Bergami et al. 2008), confers bidirectional effects on addiction-related behaviors (McGinty et al. 2010). For instance, animals that receive BDNF infusions in the VTA 2 h after a cocaine self-administration session exhibit enhanced reinstated seeking after withdrawal (Lu et al. 2004). Instead, BDNF infusion in the PL attenuates reinstated seeking as well as reinstatement-associated increases in accumbens glutamate according to the same timeline (McGinty et al. 2010). Generally BDNF undergoes activity-dependent upregulation and contributes to synapse stability and plasticity (Gomez-Palacio-Schjetnan and Escobar 2013). Interestingly, BDNF also increases astrocyte morphological complexity (Holt et al. 2019). Whether BDNF expression is altered selectively in astrocytes within corticostriatal or other circuitries pertinent to addiction and relapse or whether neuronal BDNF exerts its effects in part through astroglial signaling has not been determined.

Network Homeostasis

The coupling of astroglia through gap junctions provides them with the unique capacity to scale network activity. Although some connexin proteins are expressed at relatively high levels in the nucleus accumbens of naïve animals, connexin protein expression is reduced up to 21 days after cocaine self-administration (Bennett et al. 1999). Consistent with this finding, methamphetamine reduces gap junction coupling when delivered to cultured astroglia directly, indicated by lack of dye transfer to nearby astroglia that are normally extensively coupled (Castellano et al. 2016). The gap junction protein connexin 30 regulates excitatory synaptic strength broadly in the hippocampus by coordinating widespread synaptic insertion leading to efficient glutamate uptake through increased synaptic proximity, but not increased transporter expression (Pannasch et al. 2014). Perhaps relevant to these findings is

the discovery that inhibiting astrocytes in the medial prefrontal cortex impairs cognitive flexibility, involving coordinated neural oscillations through astroglial transmission (Brockett et al. 2018). How this may relate with flexibility in drug-related learned behaviors, such as extinction, is a relevant question given the involvement of corticostriatal glutamate in measures of drug seeking and refraining. Interestingly, blockade of gap junction proteins in astrocytes in the PL prevents extinction and reinstatement of cocaine CPP (Fitzgerald 2016). Research momentum on the involvement of gap junction proteins in addiction-related behaviors is slowly growing, and there is enthusiasm for the concept of lateral regulation by astroglia, where given their coupling, plasticity, and the multitude of mechanisms by which they impact synaptic function, astrocytes are poised to coordinate synapses that are neither directly nor indirectly linked otherwise (Covelo and Araque 2016).

Conclusions

Emerging research highlights the critical contribution of astrocytes to synaptic function, and astroglial adaptations across a number of brain regions have been shown to contribute to the encoding and expression of motivated behaviors relevant to drug addiction. A majority of early literature on astroglial function was generated in vitro and ex vivo, providing information on general astroglial responses to neural activity or pharmacological manipulation. An accumulating body of work links these early findings with in vivo behavioral measures, highlighting new avenues for research and experimentation. Here, we have highlighted research avenues poised to promote future discovery. Generation of new tools, including CalEx and viruses for astroglial labeling and functional manipulation of gene expression, and improved imaging methodologies are facilitating studies of astroglial function in rodent models of drug addiction and relapse. We expect that advances made in the coming years using these tools will drastically expand our understanding of ways in which astrocytes impact synaptic physiology during normal motivated behavior and in psychiatric disorders such as drug addiction.

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Astroglia in the Vulnerability and Maintenance of Alcohol Use Disorders

José Javier Miguel-Hidalgo

Introduction

As it can be appreciated in previous chapters of this book, a great variety of functional and structural features of astrocytes are critical to the support of neuronal metabolism, synaptic activity, myelin maintenance, and repair of the injured nervous system (Verkhratsky and Nedergaard 2018). These functions are precisely some of the most important that are pathologically disturbed by chronic or acute alcohol abuse (de la Monte and Kril 2014; Harper 2009; Kyzar and Pandey 2015; Vargas et al. 2014). Thus, it is not surprising that a large body of research on human subjects with AUDs and animal models of AUD has focused on the direct effects of alcohol on the cellular and molecular biology of astrocytes (Adermark and Bowers 2016; Verkhratsky and Parpura 2010) as well as on the roles of astrocytes in alcohol-related pathological mechanisms leading to brain damage and the establishment and maintenance of alcohol dependence (Adermark and Bowers 2016; Miguel-Hidalgo 2018). Since earlier studies on astrocytes using Golgi techniques or immunohistochemistry of cytoskeletal markers (Babu et al. 1994; Davies and Vernadakis 1984; Mayordomo et al. 1992; Popova and Shchekalina 1980; Renau-Piqueras et al. 1989), alcohol has been known to alter their morphology upon prolonged or binge exposure in developing and mature animals, although the mechanisms involved and functional consequences of those changes were not completely understood. These alterations appear to depend on the duration of the exposure to alcohol. Binge alcohol intake (or subacute exposure in astrocyte cultures) appears to cause hypertrophy of astrocyte cell bodies and processes and increased synthesis of cytoskeletal proteins such as glial fibrillary acidic protein or vimentin, while prolonged or repetitive

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exposure to alcohol may result in loss of astrocytes processes and the expression of their cytoskeletal proteins (Franke 1995; Kane et al. 1996; Sáez et al. 1991).

During neurodevelopment, most astrocytes are born after neuronal genesis ceases, so that alcohol exposure before astrogliogenesis tends to affect the generation and differentiation of neural precursors common to both neurons and glial cells, while exposure after the period of neurogenesis would mainly target the generation of astrocytes and other glial cells such as oligodendrocytes (Rubert et al. 2006), although, clearly, alcohol is still able to affect differentiation and plasticity of neurons and emerging astrocytes. In either case, alcohol exposure during pregnancy often results in developmental skeletal, neurological, and behavioral abnormalities that are grouped under the name of fetal alcohol syndrome spectrum disorder (FASD) (Saito et al. 2016; Wilhelm and Guizzetti 2015). Even in cases when the physical abnormalities of FASD are not obvious, alcohol exposure may result in behavioral disturbances associated with increased probability for later AUDs. In addition, other factors such as stress during infancy, preadolescence, and young adulthood are known to increase the chance of later alcohol abuse and dependence (Portero-Tresserra et al. 2018) or help to acquire excessive alcohol consumption (Kaufman et al. 2007; Meyer et al. 2013), probably mediated by permanent changes in neurohormones and the hypothalamic-pituitary-adrenal axis (Enoch 2011). Glial cells are sensitive to such changes and may participate in the onset and maintenance of AUDs, although the specific relevant glial responses and the mechanism of their exact putative contribution to the vulnerability to alcohol dependence largely remain to be fully understood. However, over the last decade, progress has been made in identifying a variety of mechanisms by which astrocyte dysfunction participates directly or indirectly in the onset, vulnerability, and maintenance of alcohol abuse and dependence. This chapter will address the pathological effects of alcohol exposure on the morphology and function astrocytes as well as the role that astrocyte disturbances caused by alcohol itself or other factors play in the maintenance and vulnerability to alcohol use disorders (Fig. 1).

Molecular Pathology of Astrocytes in Alcohol Use Disorders

Neuropathology of Astrocytes in Alcohol-Related Neurological Disorders

The size and morphology of astrocytes and their precursors in gray matter (GM) and white matter (WM) pathologically change in subjects with prolonged and repetitive histories of alcohol abuse (Miguel-Hidalgo and Rajkowska 2003). Some brain regions, such as the PFC and hippocampus, appear to be especially affected by alcohol-induced atrophic changes, including reduced staining of the GFAP cytoskeletal marker or lower numbers of GFAP+ astrocyte (Korbo 1999; Miguel-Hidalgo et al. 2002, 2006). Those alterations are accompanied by downregulation of

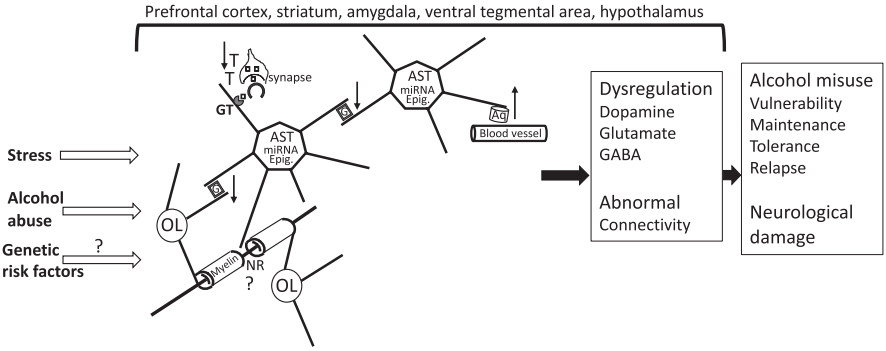

Fig. 1 Schematic illustration of several interactions of CNS astrocytes that are affected by stress, alcohol exposure, and possibly predisposing genetic factors that result not only in structural neuropathology but also in increased vulnerability to alcohol misuse by increasing tolerance and preference and favoring reinstatement of alcohol intake. The pathological interactions with astrocytes result in a variety of molecular and neurotransmitters alterations in the prefrontal cortex, ventral tegmental area, dorsal and ventral striatum, amygdala, and ventral tegmental area involving dysregulation of at least dopamine, glutamate, and GABA neurotransmission, with varying degrees of regional specificity. Alcohol exposure and other risk factors for neuropathology itself also result in pathological alterations of astrocyte-derived components at the blood-brain barrier and possibly the extracellular matrix and NRs. More recent research work has revealed epigenetic abnormalities (Epig.) or changed levels of specific miRNAs and other non-coding RNAs in alcohol use disorders that may contribute to alcohol abuse. Nevertheless, further research is needed to understand the mechanisms by which alcohol-related functional pathology at the cell and protein expression levels is linked to epigenetic and non-coding RNA markers and the involvement of astrocyte contacts at NR and oligodendrocytes that may contribute to abnormal connectivity in alcohol use disorders. Abbreviations: Aq Aquaporin 4, AST astrocytes, G gap junctions, GFAP glial fibrillary acidic protein, GT glutamate and GABA transporters, NR node of Ranvier, OL oligodendrocyte, T thrombospondin. ↑ upregulation, ↓ downregulation. Small squares at the synapse represent neurotransmitters

astrocyte-specific genes, particularly in subjects with hepatic pathology (Liu et al. 2006), indicating that indirect alcohol-related metabolic pathways must be taken into account when explaining astrocyte-related disturbances. Chronic AUDs are often concomitant with important nutritional deficiencies and hepatic pathology, causing severe neurological disorders such as Wernicke's encephalopathy, hepatic encephalopathy, or demyelinating disorders (de la Monte and Kril 2014; Verkhratsky et al. 2014). The grave neurological symptoms that accompany degeneration of GM or WM are macroanatomically detectable in the cerebral cortex, cerebellum, thalamus, or mammillary bodies (Kril and Harper 2012; Phillips et al. 1990). The cellular basis of mechanisms leading to the structural and metabolic dysfunction in those neurological disorders is not limited to oligodendrocytes or neurons but also involves importantly astrocytes (Hazell 2009), suggesting that even in subjects without major neurological signs, the alterations in emotional regulation and behavior may be dependent, at least partly on astrocyte dysfunction.

Neuropathological changes in response to alcohol abuse are not limited to alterations in number, morphology, or development of astrocytes but encompass many of

their roles in the nervous system. These roles involve calcium signaling, the balance of excitatory and inhibitory neurotransmission, regulation of neuroinflammatory processes, water balance in the CNS, as well as the regulation of dopamine-dependent behavioral processes in brain reward circuits (Adermark and Bowers 2016). The interference of alcohol actions with those roles can be understood as modifying the functions of local components of neuronal circuits with repercussions for the overall integration of nervous signals. However, alcohol-related pathology of astrocytes may also significantly disturb the connections between brain regions by directly modifying the propagation of signals in the between those regions. For instance, pathology alterations of astrocyte connexins caused by alcohol may impair the communication between astrocytes and oligodendrocytes disturbing the maintenance of myelin (Hazell 2009). Likewise, pathology of astrocytes processes and the extracellular matrix they support around nodes of Ranvier may disturb the buffering of ions in the proximity of nodes Ranvier or the aggregation of voltage-gated sodium channels. Altering ion buffering and the osmotic regulation that results from astrocyte interactions with oligodendrocytes around nodes of Ranvier causes abnormal action potential propagation in WM and myelinated portions of GM (Gankam Kengne et al. 2011).

The inhibitory action of alcohol on the proliferation and turnover of astrocytes may be a major cause for the reduction in astrocyte numbers and their functional markers. Alcohol causes significant inhibition of astrocyte proliferation and DNA and protein synthesis, including a diminution of the major astrocyte marker GFAP in cultured neonatal astrocytes (Davies and Cox 1991; Guerri 1998; Guerri and Renau-Piqueras 1997) and in astrocytes from postmortem human brain tissue (Kane et al. 1996). The reduced number of astrocytes and the shrinkage of their processes may as well impair some of their critical functions. The responses of astrocytes to chronic alcohol, although mostly inhibitory, may also lead to secondary activation of gliosis-like astrocyte responses when AUDs prolong sufficiently into senescence (Miguel-Hidalgo 2009; Miguel-Hidalgo and Rajkowska 2003). Deficits in astrocyte structure and function accumulated during aging in AUD subjects may contribute to neuronal degeneration, unleashing a secondary increase of astrocyte reactivity or gliosis, which would be reflected in increased GFAP production and gliosis, although it is still unclear how other markers of astrocytes respond to aging-associated neuronal degeneration. The response to acute alcohol exposure also may involve extensive activation gene expression for more fundamental pathways linked to cellular stress such as the heat shock response (Pignataro et al. 2013).

The cycle of alcohol abuse is considered to depend not solely on the rewarding properties of alcohol and the involvement of altered dopaminergic transmission but on the negative behavioral and organic consequences upon withdrawal from alcohol intake (Koob 2013). Aversion to these consequences reinforces the behaviors leading to excessive alcohol consumption and favors relapse and the maintenance of alcohol abuse and addiction (Gilpin and Koob 2008). The aversion to the unpleasant consequences of withdrawal seems to greatly depend on the activation of neurons and the expression of glucocorticoid and CRF receptors in the amygdala (Gass et al. 2011; Gilpin and Roberto 2012; Koob 2009; Läck et al. 2005; Patkar et al. 2016;

Vendruscolo et al. 2012) after chronic alcohol abuse, although other brain regions are also recruited in changes leading to reinstatement of drinking (Schroeder et al. 2008). Disturbances of neurotransmission in the amygdala are attributed to mostly neuronal pathology; however, some postmortem studies have shown that one of the most distinctive changes associated with chronic alcoholism in the basolateral amygdala is the reduction of glutamate transporters GLT1 and GLAST, the two major transporters for glutamate expressed by astrocytes (Kryger and Wilce 2010). Gene expression changes also occur in the amygdala that involve several pathways present n astrocytes and other glia (McBride et al. 2014); for some of which, there is evidence supporting a role in the vulnerability or maintenance of behaviors of alcohol addiction (Lee et al. 2013; Nam et al. 2012; Paul and Medina 2012).

Alcohol Effects on Glutamate Receptors and Astrocyte Components of the Cycle for Release and Reuptake of Glutamate

A major tenet of the theories explaining the neurobiological underpinnings of the vulnerability to alcohol abuse is that, initially, repetitive or binge exposure to alcohol causes excessive activation of reward pathways mediated by increased release of dopamine in the nucleus accumbens and the prefrontal cortex by synaptic terminals of dopaminergic neurons with cell bodies located in the ventral tegmental area (VTA) (Boileau et al. 2003; Brodie et al. 1999; Cowen and Lawrence 1999; Heinz et al. 2009; Pascual et al. 2009; Tupala and Tiihonen 2004). VTA dopaminergic neurons are negatively regulated by synapses formed with axon terminals of interneurons that release gamma-aminobutyric acid (GABA). GABA release from these terminals in turn is inhibited by opioids acting on presynaptic GABAA receptors (Koob et al. 1998). Given the critical role of astrocytes in the synaptic reuptake of inhibitory and excitatory neurotransmitters in all the implicated structures (VAT, NACC, PFC) (Ayers-Ringler et al. 2016; Forget et al. 2006; Fouyssac and Belin 2019; Gomez et al. 2019; Haydon et al. 2009; Schwarcz et al. 1994; Vollbrecht et al. 2014; Xin et al. 2019), it seems natural to think that there is a role for astrocytes in the altered regulation of the effects and release of neurotransmitters, including dopamine, in alcoholism (Deng et al. 2009; Flatscher-Bader et al. 2007; Morikawa and Morrisett 2010; Trantham-Davidson and Chandler 2015; Volkow et al. 2007; Xiao et al. 2009) and thus in the corresponding disturbances of function and behavior linked to them. The participation of astrocytes in the vulnerability to AUD, thus, may involve direct actions of alcohol exposure on astrocytes or indirect effects by first causing neuronal, microglial, or oligodendroglial physiological disturbances that impinge on astrocyte function, which in turn further modifies neuronal function and behavioral outcomes. In addition, abnormalities of astrocyte gene expression or physiology preceding AUDs, including developmental disturbances, may exist that

increase the vulnerability to alcohol abuse and may or may not involve the same astrocytic pathways affected by AUD-promoting alcohol exposure.

AUDs and the Role of NMDA-Type Glutamate Receptors

The available evidence points to an increase, at least in some brain regions, in the content of NMDA-type glutamate receptors and a decrease in GABA receptors, particularly in chronic alcoholism (Davis and Wu 2001) which would be at the root of further changes in dopamine release in acute and chronic alcohol exposure and thus importantly contribute to craving, tolerance, and dependence. Ethanol acts as an antagonist of the actions of glutamate at NMDA receptors. Chronic alcohol consumption leads to enhanced expression of NR2A, NR2B, and NR1 NMDA receptors in the neocortex and the hippocampus (Gass and Olive 2008; Nixon et al. 2004), which would account for increased neuronal excitability that occurs after alcohol withdrawal in animal models. However, more variable, human studies in chronic alcoholics demonstrate higher NMDA receptor ligand binding (Tsai 1998; Tsai et al. 1998) in the PFC, but not in other brain regions including the cingulate cortex, hippocampus, and cerebellar vermis (Freund and Anderson 1996; Freund and Anderson 1999). mRNA levels for the same NMDAR subunits are unchanged in uncomplicated alcoholics but are lower in AUD subjects with cirrhosis (Ridge et al. 2008).

AUDs and the Release of NMDA Receptor Co-agonists by Astrocytes

One of the best-known pharmacological effects of ethanol is its antagonism of the activation of NMDA receptors by the neurotransmitter glutamate. In animal models of chronic alcoholism, there is also an increase in the expression of glutamate receptors that may explain increased behavioral agitation and neuronal hyperexcitability following withdrawal form alcohol intake (Gass and Olive 2008). These withdrawal effects act as negative reinforcers to facilitate relapse into alcohol drinking. NMDA receptor activation by glutamate is also dependent on the binding of co-transmitter glycine to a specific site (different from that for glutamate) of the receptor. Astrocytes release D-serine, which specifically binds the glycine site of NMDA receptors and thus can regulate their activation state (Tsai 1998). Thus, astrocyte integrity may directly affect the effects of ethanol on neuronal excitability and consequently on the probability to engage in alcohol abuse. Interestingly, ethanol competes with D-serine for the occupancy of the glycine-site, which would further amplify the effects of astrocyte inability to provide D-serine, helping to explain the development of reduced sensitivity to ethanol effects in mice (Kiefer et al. 2003) or

increased tolerance to partial agonists of the glycine site in AUD subjects (Krystal et al. 2011).

Astrocytic Glutamate and GABA Transporters and Glutamine Synthetase in the Vulnerability to Alcohol Abuse

Alcohol is known to block glutamate NMDA receptors and potentiate the activation of GABA receptors and thus contribute to the neurotropic responses to alcohol. Those actions of alcohol result in alterations of glutamate and GABA release and their concentrations in the peri-synaptic space, where astrocytes regulate extracellular GLU and GABA by uptake with specific transporters lodged in their cell membranes. In addition, the neurotransmitters taken up by astrocytes are recycled first by converting glutamate into glutamine through the action of the astrocyte-located enzyme glutamine synthetase. Thus, the ability of astrocytes to regulate the neurotransmitters around synapses may be affected by changes in the transporters or glutamine synthetase. In fact, studies of the mRNA and protein levels as well as the distribution of glutamate transporters and glutamine synthetase have been performed in the neocortex of AUD subjects (Ayers-Ringler et al. 2016; Miguel-Hidalgo et al. 2010). However, these studies have not detected significant chronic alcohol abuse-associated changes in protein levels of either EAAT1, EAAT2, or GS caused by prolonged alcohol exposure, while in vitro studies rather have shown that alcohol treatment may lead to an increase in the rate of glutamate transport per astrocyte (Smith 1997; Smith and Zsigo 1996; Zink et al. 2004), although in some rat brain areas such the nucleus accumbens, there appears to be an ethanol-induced decrease in glutamate transport that still is not linked to a reduced expression of glutamate transporters (Melendez et al. 2005). Nonetheless, in alcohol self-administering animals, we have observed that withdrawal of the access to alcohol results in increased glutamine synthetase immunoreactivity in the rat PFC, although the role of such an increase in the mechanisms of relapse or maintenance of alcohol intake remains to be ascertained.

Previously we have argued that unaltered or increased expression of glutamate receptors or transporters in several brain regions of AUD subjects may depend on the severity of the neural damage caused by alcohol exposure, because in a cohort of AUD subjects with comorbid major depression (unlike “non-complicated” alcoholics), we found reduced levels of glutamate transporters and GS, suggesting the possibility that more severe alcohol-related pathology actually dampens the expression of glutamate cycle constituents in astrocytes (Hazell et al. 2010; Miguel-Hidalgo et al. 2010). Alternatively, if initial damage is not important in “uncomplicated” AUD subjects, there might be compensatory mechanisms in astrocyte components of the glutamate cycle. For instance, astrocytic glutamate transporter levels (Wu et al. 2011) can increase even if alcohol itself blocks the activation of those transporters (Mulholland et al. 2009). Nevertheless, regulation of glutamate

transporter gene expression may partake in the vulnerability to alcoholism because mice lacking the astrocyte glutamate transporter GLAST do not develop place preference for alcohol and show diminished voluntary alcohol consumption as compared to control mice (Karlsson et al. 2012). Likewise, intracerebral blockade of GLT-1 reduced binge ethanol drinking in mice (Smith et al. 2014). In other less studied parts of the brain, but gaining importance for their involvement in the regulation of alcohol intake, such as the suprachiasmatic nucleus, the contribution of astrocytic transporters to abuse behaviors may be instrumental since enhancement of GLT-1-based glutamate transport with ceftriaxone diminishes alcohol drinking (Lee et al. 2013), while reduced astrocytic GLT-1 resulting from deletion of the circadian period gene (Per2) in mice leads to augmented alcohol intake (Spanagel et al. 2005).

Gap Junctions of Astrocytes in AUDs

Astrocytes are capable of communication among themselves and with oligodendrocytes and neurons through gap junctions. These junctions include groups of channels connecting the cytoplasms of two cells. Each gap junction channel is formed by two connexons composed of six protein subunits each, with two connexons (one for each cell forming the junction) forming a gap junction. The subunits in each connexon are cell-type specific. In the CNS, astrocyte connexons are mainly formed with connexin 43 (Cx43) or connexin 30. Gap junctions allow for fast communication of calcium signals between astrocytes, the buffering of potassium, the diffusion of small molecules, and the passage of water exchanged with the blood circulation. They also allow for the exchange of intracellular signals with oligodendrocytes that are important in the maintenance of myelin.

Prolonged alcohol exposure also appears to reduce the localization of Cx43 to the cell membrane in astrocytes and other cells (Miguel-Hidalgo et al. 2014; Wentlandt et al. 2004). This reduction may have significant effects on the ability of astrocytes to spread calcium transients. In addition, Cx43 is also the major constituent of hemichannels (connexons sitting on the membrane not coupled to connexons in adjacent cells) that are involved in the release of molecules such as ATP and D-serine to regulate calcium signals between astrocytes and glutamate receptor in neurons. Alterations in the extracellular concentrations of those molecules may directly affect neurotransmission in brain regions such as the prefrontal cortex, the ventral tegmental area (VTA), and nucleus accumbens (NAcc) and thus increase the vulnerability to abuse alcohol. For instance, D-serine is a co-transmitter that greatly enhances the actions of glutamate at NMDA receptors, so that reduced release because of limited Cx43 hemichannel numbers may contribute to enhanced activation of the reward circuits, due to the inactivation of inhibitory neurons that control the activity of dopaminergic neurons in the VTA. In the prefrontal cortex of human subjects with AUDs, we have found a dramatic decrease of immunohistochemical staining and protein levels for Cx43 (Miguel-Hidalgo et al. 2014). Since the

prefrontal cortex is a major site for pathology in AUD subjects, and is heavily involved in emotional and appetitive control, the alteration of Cx43 may contribute to the vulnerability to and the maintenance of AUDs. In fact, we found that localized infusion of a gap junction/hemichannel inhibitor or an astrocyte-directed toxin in the prefrontal cortex of the rat increased transiently but significantly alcohol intake in rats (Miguel-Hidalgo et al. 2009). Further involvement of an alcohol-induced reduction of astrocyte gap junction hemichannels in increasing the vulnerability to alcohol abuse is suggested by the pharmacological blockade of hemichannels, which enhances the motivation to drink alcohol after 3 weeks of abstinence from alcohol (Bennett et al. 2003; Bull et al. 2014). Nonetheless, the exact role of astrocyte gap junctional changes in regulating AUDs in adults remains to be fully elucidated since prenatal exposure to ethanol, which increases the probability of epilepsy in humans and in young mice, results in increased connexins 43 and 30 in the hippocampus and cortex of these mice (Ramani et al. 2016). Whether these early astrocyte-related changes have any bearing on the expression of AUDs later in life will require further study.

Involvement of Astrocytes in Neuroimmune Responses Elicited by Alcohol Exposure

Astrocytes are capable of releasing cytokines and other inflammatory factors involved in neuroimmune signaling and, conversely, they respond to neuroimmune signals (Warden et al. 2016). In addition, astrocytes carry toll-like like receptors in their cell membrane. These receptors mediate neuroimmune responses to a variety of signals. Exposure to excessive ethanol induces the release of inflammatory mediators from glial cells, including astrocytes, and binding of those molecules to TLRs further facilitates cytokine release and the activation of inflammatory responses (Alfonso-Loeches et al. 2010, 2012; Montesinos et al. 2016). Recent research suggests that signaling at TLR4 in the prefrontal cortex may have a direct role in the vulnerability to and maintenance of alcohol intake. While wild-type adolescent mice increase the rate of alcohol consumption over time, knockout mice lacking TLR4 do no escalate alcohol drinking, pointing to the possibility that activation of TLR4 receptors in astrocytes participates in facilitating alcohol drinking after exposure to alcohol (Montesinos et al. 2016).

Astrocyte Thrombospondin in AUD-Related Synaptic Alterations

Reduced numbers of synaptic contacts and structural alterations of pre- and presynaptic components are also caused by excessive or chronic alcohol intake. Besides the roles of peri-synaptic astrocyte processes in the recycling of neurotransmitter

and the regulation of their actions, astrocytes are known to secrete factors, such as thrombospondins, that are involved in the maturation and formation of synapses. Impairments to the role of astrocytes in secreting thrombospondins or alterations of their receptors can result in deficient synaptic function and formation (Ullian et al. 2004). In animal models, alcohol exposure can result in persistent reduction of thrombospondin release in addition to impaired matching of presynaptic and postsynaptic structures (Risher et al. 2015). Liver damage in alcoholism may also result in synaptic dysfunction mediated by astrocytes, because increased ammonia levels reduce astrocyte-released thrombospondin and levels of synaptic proteins (Jayakumar et al. 2014). Alcohol exposure during early or prenatal stages of development, and maybe later too, may cause persistent changes in synapse formation involving thrombospondin (Trindade et al. 2016). Other factors secreted by astrocytes to the extracellular matrix such as laminin or heparan-sulfate proteoglycan are also reduced by alcohol exposure (Lasek 2016; Trindade et al. 2016). In summary, repeated alcohol exposure at different stages of prenatal and postnatal development may result in abnormal regulation of astrocyte-released factors that participate in synaptogenesis.

Astrocyte Processes at the Blood-Brain Barrier and the Involvement of Aquaporins in AUD-Related Neuropathology

The endings of astrocyte processes distal to their cell bodies tightly sheath the basal lamina around the endothelial cells of small blood vessels, so contributing to the maintenance of the blood-brain barrier (BBB) (Prat et al. 2001). Moreover, those processes are critically involved in the exchange of metabolic mediators with the circulating blood and to the control of blood flow (Koehler et al. 2009). Chronic alcoholism BBB components cause disruption (Haorah et al. 2005; Rubio-Araiz et al. 2017), impairing the exchange of metabolites such as glucose and trophic factors, which potentially affects the function of surrounding neurons and glial cells (Abdul Muneer et al. 2011a, b).

Effects of alcohol mediated by astrocytes at the BBB are likely to involve changes in aquaporins as well (Kong et al. 2013), in particular aquaporin 4 (AQ4), a membrane protein highly expressed in astrocytes processes abutting at the BBB that allows passage of water through the cell membrane (Badaut et al. 2002; Rajkowska et al. 2013). Repeated alcohol binging in rats results in higher aquaporin levels, swelling of astrocytes, and activation of neuroinflammatory factors (Collins et al. 2013; Collins and Neafsey 2012). Anti-inflammatory treatments can prevent the effects of the AQ4 elevation that is concomitant with increases in neuroinflammatory markers (Tajuddin et al. 2014). Aquaporin loss in astrocytes may contribute to the loss of myelin in central pontine myelinolysis, although more research seems to be needed to fully ascertain this possibility (Popescu et al. 2013).

Alcohol-induced AQ4 increase in astrocytes of the NAcc and the concomitant cell swelling may contribute to increased vulnerability to excessive alcohol intake because the upregulation of the dopamine level in the NAcc is positively correlated with the concentration of AQ4 (Kuppers et al. 2008; Lee et al. 2013), and inhibition of cell swelling results in the inhibition of ethanol-induced dopamine release (Adermark et al. 2011a).

Epigenetic Changes in Astrocytes in AUDs

mRNA transcription from DNA is heavily regulated by epigenetic modifications such as acetylation and methylation of DNA itself, the associated chromatin histones, or both (Graff et al. 2011). Translation of mRNA into proteins is further regulated by the presence of noncoding fragments of microRNAs (miRNAs) that are about 22 nucleotides long and bind to complementary sequences in mRNA to impede translation of specific proteins (Emery and Lu 2015; Li and Yao 2012; Liu and Casaccia 2010).

Various studies have revealed that the development of astrocytes and other glial cells depends on an intricate network epigenetic pathways (Bian et al. 2013; Emery and Lu 2015; MacDonald and Roskams 2009; Namihira and Nakashima 2013). The fate and differentiation of precursors into astrocytes are dependent on methylation of DNA at specific nucleotides and on specific histone modifications (Moyon et al. 2016). In fact, alcohol exposure can significantly disturb epigenetic pathways, suggesting that pathology of astrocytes and their dysfunction may depend on enduring, long-term changes in gene expression in the components of both regulatory and effector intracellular pathways (Alfonso-Loeches et al. 2012; Aspberg and Tottmar 1994; Bichenkov and Ellingson 2009; Coutts and Harrison 2015; Creeley et al. 2013; Newville et al. 2017).

There is limited knowledge on the effects of alcohol exposure on astrocyte epigenetic modifications and the expression of proteins and pathways affected by those modifications. However, available evidence raises the possibility that alcohol exposure causes persistent epigenetic and gene expression changes in astrocytes. For instance, prenatal ethanol exposure in rats produces hypermethylation of the promoter for the astrocyte GFAP gene leading to diminished GFAP expression during postnatal development (Vallés et al. 1997).

Astrocyte Epigenetic Markers

AUDs result in extensive changes of brain epigenetic markers (Farris et al. 2015; Legastelois et al. 2017; Weng et al. 2015; Zhou et al. 2011) and higher levels of miRNAs regulating the expression of several proteins (Lewohl et al. 2011). Alcohol induces epigenetic alterations of DNA methylation and in methylation and

acetylation of histones in the human PFC, hippocampus, and amygdala (Farris et al. 2015; Ponomarev 2013) as well as in cultured astrocytes (Zhang et al. 2014). Some research indicates that alcohol intake causes inhibition of histone deacetylase (HDAC) in the amygdala leading to increased histone acetylation and reduced anxiety, while withdrawal, anxiety, or alcohol exposure in adolescence would be rather linked to increased HDAC activity (Pandey et al. 2017) and low acetylation (Pandey et al. 2008). Since acetylation level is inversely related to gene expression, higher HDAC would result in lower expression of genes associated with synaptic plasticity. In consequence, HDAC inhibitors have been insinuated as therapeutic agents to mitigate anxiety and alcohol intake (Pandey et al. 2017). Other research has found mainly DNA methylation reductions in humans with AUDs, although a recent study used a different methodology and found a higher proportion of hypermethylated sites in brain DNA of AUD subjects (Tulisiak et al. 2017).

DNA methylation depends on the activity of DNA methyltransferases (DNMTs). In experimental animals, prolonged alcohol intake induces high DNMT levels, but in the human brain, overall methylation changes are rather associated with lower DNMT mRNA (Tulisiak et al. 2017). Nonetheless, DNA methylation patterns in AUDs are complex and include both de- and hypermethylated promoters of particular genes (Tulisiak et al. 2017). Thus, in view of the higher DNMT level in experimental models of AUDs, some researchers have attempted to leverage DNMT inhibition as a possible therapeutic approach for AUDs. These investigators have discovered that the DNMT inhibitors 5-aza and decitabine can reduce excessive alcohol drinking in rodents (Ponomarev et al. 2017; Tulisiak et al. 2017). In mice, these behavioral changes are paralleled by increased expression of genes preferentially present in astrocytes in the VTA (Ponomarev et al. 2017). DNA methylation and other epigenetic markers in the developing CNS (Laufer et al. 2017; Mahnke et al. 2017; Ozturk et al. 2017) are also disturbed as a consequence of early alcohol exposure.

Research on the effects of ethanol on cultured astrocytes has also found increased methylation in the promoter of the tissue plasminogen activator (Tulisiak et al. 2017), which is involved in the degradation of components of the extracellular matrix and has been found upregulated in animal models of AUDs (Zhang et al. 2014). In rats, prenatal ethanol exposure leads to hypermethylation of the promoter for the astrocyte-expressed GFAP gene and to reduction in GFAP expression during early postnatal development (Vallés et al. 1997). These findings suggest that alteration of DNA or histone epigenetic markers in astrocytes may play an important role in mediating behavioral disturbances in AUDs, although it is unclear whether alterations during early development or later, as a consequence of alcohol abuse, are etiologically related to increased vulnerability to alcohol abuse and whether particular brain structures are related to that vulnerability.

Variety of Mechanisms Involving Astrocytes in the Vulnerability to AUDs

Plasticity in the morphology of astrocytes processes and in the expression of their cytoskeletal proteins has been directly linked to physiological and behavioral processes, and is maybe related to resumption of alcohol intake after a period of abstinence. In particular, increases in the number of GFAP-positive astrocytes or in the morphology of processes in the NAcc are observed after 3 weeks of abstinence from alcohol self-administration and are parallel to increases in the motivation to drink ethanol (Bull et al. 2014). Given the importance of astrocytes in the regulation of synaptic activity in the NAcc, relapse to alcohol self-administration may well depend, at least partly, on the numbers and morphology of astrocytes involved in such regulation. Interestingly, the effects of excessive alcohol exposure on NAcc astrocytes may also influence other appetitive behaviors as shown recently in female mice undergoing several days of chronic intermittent alcohol exposure. In these experiments, extinction of conditioned place preference for food rewards was reduced in alcohol-dependent animals in parallel with a reduction in the GFAP staining of astrocytes in the NAcc (Giacometti et al. 2020). At the same time, selective DREADDS-based chemogenetic activation of NAcc astrocytes restored extinction of food CPP in alcohol-dependent animals, suggesting that NAcc astrocyte activity is involved in the regulation of appetitive behaviors and in the effects of alcohol on the expression of those behaviors. Likewise, in the prefrontal cortex of rats abstinent from prolonged alcohol intake, glutamine synthetase immunoreactive (GS-I) astrocytes are increased (Miguel-Hidalgo 2006). These animals also show an increased rate of alcohol consumption (as compared to before abstinence), suggesting that an increased glutamate processing ability by newly recruited GS-I astrocytes in the PFC may contribute to a relapse into excessive alcohol drinking.

Despite the effects of early alcohol exposure on astrocyte numbers and astrocytic proteins, a form of early-life stress, maternal separation, although increasing the chance for enhanced alcohol seeking behavior in rats, does not appear to cause changes in the numbers GFAP-immunostained astrocytes or in the length of their processes in the hippocampus. This effect occurs despite the ability of maternal separation to also increase neuronal numbers in the amygdala but decrease them in the dentate gyrus of the hippocampus (Gondre-Lewis et al. 2016), suggesting that there are differential pathways of astrocyte involvement in the contribution to AUDs.

Various mechanisms with components localized at the cell membrane or intracellularly, some of which have been mentioned above, result in dramatic changes in the concentration of calcium within astrocytes. The membrane mechanisms include receptors to various neurotransmitters and growth factors, while the spread of calcium t increases to adjacent astrocytes involves gap junctions. One of the main mechanisms to increase calcium within astrocytes depends on the activation of GqGPCRs. Expression of genes for G-protein-coupled receptors and calcium regulation is decreased by sustained exposure to alcohol, but acutely, alcohol activates GqGPCR resulting in increased intracellular calcium in astrocyte and augments

release of ATP, which once rapidly converted into adenosine acutely contributes to behavioral alterations such as hyperlocomotion and sedation (Erickson et al. 2018; Guerra-Gomes et al. 2017). In recent work, Erickson et al. (2020) using a chemogenetic approach have shown that stimulation of calcium signals in astrocytes increases alcohol consumption and preference but that reduction of intracellular calcium in those cells reduces alcohol intake (Erickson et al. 2020). In addition, GqGPCR activation in PFC astrocytes potentiates sensitivity to acute hyperlocomotion and the subsequent sedation caused by alcohol, but blockade of astrocytic calcium increases has the inverse effect (Erickson et al. 2020). These effects are dependent on the release of ATP, because blockade of the adenosine receptor A1R reduces the enhancement of alcohol intoxication caused by the chemogenetic activation of the Gq subunit of GPCR in astrocytes (Erickson et al. 2020; Moffat and Ron 2020). These experiments indicate that the ability of alcohol to alter calcium signaling in astrocytes of brain regions relevant to addiction, such as the prefrontal cortex, may be an important determinant of the vulnerability to alcohol abuse.

As somewhat hinted above, several of the mechanisms pathologically targeted in astrocytes by excessive (binge or chronic) alcohol intake not only affect negatively neuronal function, and thus indirectly behavior, but may be major mediators for further and sustained alcohol dependence and abuse. For instance, the increase in the density of GFAP-positive astrocytes in the nucleus accumbens shell during abstinence in rats is positively correlated with the motivation to retake alcohol self-administration (Bull et al. 2014). The effects of deficient metabolic function in astrocytes caused by ethanol exposure may also play a role in facilitating alcohol self-administration, since infusion of fluorocitrate, a metabolic inhibitor mainly taken up by astrocytes, in the prefrontal cortex temporarily increases preference for alcohol intake, which could be mediated by reduced taurine release by astrocytes, because taurine release can be inhibited by fluorocitrate (Choe et al. 2012). By contrast, swelling of astrocytes in the nucleus accumbens, another consequence of alcohol exposure (Adermark et al. 2011a; Vargova and Sykova 2014), results in the release of taurine, involved in the release of various neurotransmitters including dopamine in the NAcc, resulting in activation of dopamine D1 and D2 receptors, which are involved in the reinforcing properties of alcohol and other drugs.

Recent studies also point to an involvement of the astrocyte cystine-glutamate antiporter function in the vulnerability to alcohol dependence since reduced content of the antiporter in the medial prefrontal cortex results in resistance to alcohol-induced conditioned place preference and facilitates stress-induced reinstatement of CPP for alcohol in rats (Amaral et al. 2020).

In addition to altered astrocyte function in the prefrontal cortex and nucleus accumbens favoring reinstatement and facilitating self-administration, pathology of astrocytes in the dorsomedial striatum (DMS) may be involved in the establishment of habitual reward-seeking behavior. Experiments in a rat model have shown that calcium increases in DMS astrocytes induced with chemogenetic technology cause a change from habitual behaviors to goal-directed behaviors that is mediated by astrocyte adenosine metabolism (Kang et al. 2020). These results are relevant because alcohol exposure is associated with alterations in the capacity of astrocytes to elicit calcium transients, which are dependent on the neurotransmitters astrocytes

are exposed to around synapses (Catlin et al. 2000; Kimelberg et al. 1993; Salazar et al. 2008). At the same time, intercellular communication through gap junctions that allow for the spread of Ca++ transients in astrocyte networks may also be inhibited by ethanol (Adermark et al. 2004), which could be further complicated by ethanol-associated reduction of astrocyte-expressed connexins that form gap junctions and hemichannels.

The abnormal regulation of intracellular calcium levels in astrocytes by altered activation of A1 adenosine receptors may as well contribute importantly to the regulation of alcohol intake and to the sedative effects of alcohol. In mice, activation of calcium signaling by G-protein-coupled receptors in astrocytes of the prefrontal cortex results in increased ethanol consumption in alcohol-naïve mice but not in ethanol addicted mice, which suggests that calcium regulation within astrocytes contributes to the establishment of alcohol abuse and possibly to the tolerance to alcohol effects (Erickson et al. 2020). In addition, A1 adenosine receptors in astrocytes were shown to participate significantly in the sedative effects of alcohol. Thus, the various effects of ethanol impinging on the regulation of intracellular calcium changes in astrocytes would further contribute to the maintenance of excessive alcohol intake.

Effects of Early Alcohol Exposure and Stress on Astrocyte and Their Role in AUDs

Various prenatal and postnatal disturbances of neural development increase the vulnerability to drug abuse or dependence including alcohol abuse (Campbell et al. 2009). Since those disturbances include pathological changes of glial cells, in particular astroglia (Guerri and Renau-Piqueras 1997), it is possible that the increased vulnerability depends partly on anomalous generation of astrocyte precursors and astrocytes during gliogenesis or damage to newly differentiated astrocytes that would play roles in the development of neurons and oligodendrocytes, including myelin formation by the latter. These developmental glial alterations are involved in the structural, cognitive, and behavioral abnormalities that characterize fetal spectrum disorder (Guizzetti et al. 2014; Wilhelm and Guizzetti 2015). However, the specific roles that the developmental deficits in astrocyte formation play in leading to increased probability to alcohol abuse and dependence in adolescence and adulthood are still unclear.

The grave features of fetal alcohol spectrum disorders and, in general, of prenatal and early postnatal alcohol exposure are not limited to generalized physical, cognitive, and psychiatric consequences, but also may induce dramatic increase in the probability of promoting alcohol abuse in those subjects involuntarily exposed to alcohol early in development. In fact, it seems that for many adolescents and young adults, early alcohol exposure is a better predictor of later abuse than the history of alcohol problems per se (Baer et al. 1998, 2003; Miller and Spear 2006). Given the roles of astrocytes in induction, reinstatement and maintenance of alcohol abuse

mentioned earlier, and the known negative consequences of early alcohol exposure on glial cell development (Wilhelm and Guizzetti 2015), it is very likely that early alcohol-related pathology of astrocytes and the processes they support (such as myelination) may contribute to set the stage for adolescent or adult acquisition of alcohol abuse disorders. Consistent with this view are studies showing that even moderate prenatal ethanol exposure in rats can result in significant alterations of GFAP and astrocytic glutamate transport when measured during the adolescence of the exposed rats (Brolese et al. 2014, 2015).

Early stress is a factor for later engagement in behaviors of addiction including alcohol abuse (Gondre-Lewis et al. 2016; Penasco et al. 2015). A possible role for astrocytes in early stress-linked abuse liability is consistent with studies in rats subjected to maternal separation; after which, they present altered content of astrocytic CB1 receptors, which are known for their involvement in the regulation of behaviors of addiction (Lopez-Gallardo et al. 2012). These rats also develop increased alcohol drinking and reduction of endocannabinoid levels in the striatum and prefrontal cortex (Portero-Tresserra et al. 2018), thus suggesting that an abnormal role of astrocytes in endocannabinoid neurotransmission alterations caused by early stress may contribute to development of AUDs (Adermark et al., 2011b; Karlsson et al., 2012). In addition, early-life stress can also result in anomalous function of hypothalamic astrocytes, which has been linked to susceptibility to stress during adulthood, a risk factor for AUDs (Gunn et al. 2013).

A multitude of epigenetic changes have been identified in the brain as a consequence of FSAD-inducing exposure to alcohol (Lussier et al. 2017). Those changes affect many pathways involved in neuronal plasticity and survival. Some changes that affect glial cells such as DNA hypermethylation of the GFAP gene indicate that astrocytes may undergo long-lasting gene expression changes that may affect later alcohol consummatory behavior (Basavarajappa and Subbanna 2016; Vallés et al. 1997), although experiments are needed to further ascertain this possibility.

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Part V
Astroglia in Eating Disorders

Brain Volume Loss, Astrocyte Reduction, and Inflammation in Anorexia Nervosa

Jochen Seitz, Stefanie Trinh, Vanessa Kogel, and Cordian Beyer

Introduction

Anorexia nervosa (AN) is characterized by strongly reduced weight or insufficient development-adapted weight gain while feeling overweight (body image distortion), being afraid of gaining weight (weight phobia) and often accompanied by increased physical activity. It is the third most common chronic illness in adolescent patients and has a lifetime prevalence of 0.5–1% and the highest mortality of all psychiatric diseases (Gonzalez et al. 2007). Incidence appears to be on the rise, and first-onset patients become younger and younger (Smink et al. 2012; Steinhausen and Jensen 2015). Exact etiology remains unclear but includes a strong genetic component explaining about 60–70% of the variance, coupled with weight loss due to dieting or supposedly "healthy diets" or excessive sport with insufficient energy intake. Character traits like perfectionism, anxiety, insecurity, and poor self-insight as well as societal influences of slim body ideals appear to have additional effects. AN has a strong gender imbalance of 10–15 females vs 1 male (Herpertz-Dahlmann 2015), which also remains poorly understood. Patients and relatives often suffer extensively and enduringly during this often chronic disease (average illness duration is 6 years (Darby et al. 2009)), with major implications for healthcare resources. Semi-starvation as experienced by patients with AN also has many endocrine consequences: decreased thyroid function to conserve energy, increased cortisol level associated with the stress of the disease, altered hunger and satiety hormones like increased levels of ghrelin and reduced levels of leptin and amenorrhea with a reduction in sex hormones, and a delay of pubertal development and growth as well as related osteopenia and later osteoporosis due to lack of estrogen

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(Herpertz-Dahlmann 2015). Chronically ill patients, especially after more than 3 years of illness, increasingly show neuroprogessive changes with neuropsychological deficits including mental rigidity and inflexibility, learning impairments, and reduced visuospatial skills and traits reminiscent of autism (Treasure and Willmott 2020).

Brain Volume Reduction

One of the most striking somatic consequences of AN is a severe brain volume loss that appears to affect all brain structures (Seitz et al. 2016; Seitz et al. 2018). Its cause remains largely elusive; however, astrocyte reduction might play an important role in its pathophysiology. This "pseudoatrophia cerebri" is so extensive, it can be detected with the bare eye when reading MRI scans of the brain (see Fig. 1) and encompasses 3.7% brain volume loss in gray matter and 2.2% in white matter in adult patients and 7.6% in gray and 3.2% in white matter in adolescents. The extra space created intracranially by the retracting brain is reactively filled by CSF that is increased by 12.8% and 22.8%, respectively (for a recent meta-analysis, see Seitz et al. 2018).

Brain volume loss was functionally related to drive for thinness (Joos et al. 2010) and dietary restraint (McCormick et al. 2008), reductions in visuospatial skills (Castro-Fornieles et al. 2010), perceptual organization, and reasoning skills (McCormick et al. 2008). Brain volume reduction was also associated with this prognosis: Our own study found white matter volume reduction and cerebellar pseudoatrophy to be predictive of reduced body weight at 1- and 2.5-year follow-up – a frequently used proxy for clinical outcome – explaining an additional 20% of variance above known predictors like body mass index (BMI) at admission and illness duration (Seitz et al. 2015). McCormick et al. (2008) found incomplete brain

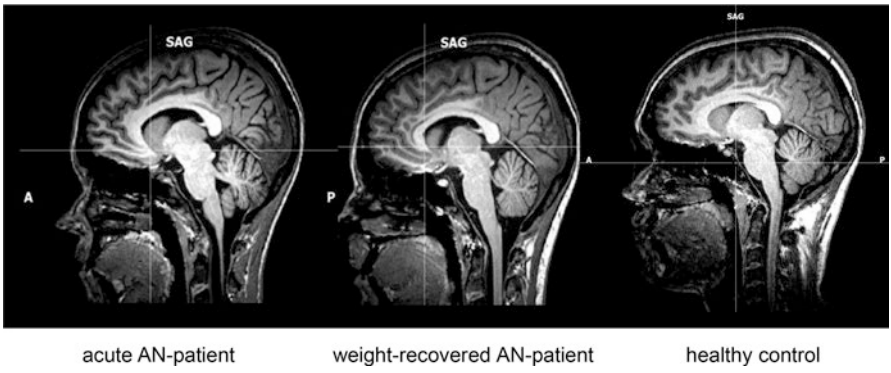

Fig. 1 Cerebral MRI images of a patient with acute AN (left), the same patient after short-term weight recovery (middle), and a healthy control (right). Note the brain volume reduction visible to the bare eye, evidenced by reduced gyri, while the sulci and ventricles are enlarged. (From Seitz et al. 2016 JNT with permission)

volume normalization upon short-term weight recovery to be predictive of relapse at 1 year (McCormick et al. 2008). Hope comes from data of short- and long-term recovered patients with about on average 50% of the brain volume reduction being reinstated after short-term weight recovery already (after about 4–6 months of treatment). Following long-term recovery (>1.5 years with normal weight), only about 0.5% of gray and 1% of white matter reductions remained in the meta-analysis, which did not reach statistical significance anymore, so it remains unclear whether some scarring and residual brain volume reduction remains or recovery is complete (Seitz et al. 2018). Importantly, this only applies for recovered, weight-restored patients – those chronically ill and underweight remain with a shrunken brain and all of its consequences.

Potentially Underlying Pathophysiology of Brain Volume Loss and the Role of Astrocytes

A systematic analysis of potential factors influencing brain volume reduction showed that absolute low BMI was most predictive, followed by BMI loss (Seitz et al. 2015). Two more studies with more chronically ill patients could also show the effect of extensive illness duration on gray matter volume reduction (Boghi et al. 2011; Fonville et al. 2014). Also regarding its reversibility upon weight gain, brain volume reduction thus appears to be a closely linked state marker for starvation. A potential confounder could be the hydration status which is known to influence also brain volumes. However, multiple studies have analyzed dehydration parameters in urine and blood serum and all do not support an influence of general (de-)hydration on brain volume reduction in AN (King et al. 2018; King et al. 2015; Vogel et al. 2016). It is interesting that gray and white matter reductions are much more pronounced in adolescents compared to adults; the still developing brain of adolescents appears to be more vulnerable. In the adolescent brain, normally, multiple developments take place in parallel that might be of importance for this process. For one, increased synapse formation in the early years is followed by pruning of unused and thus unnecessary synapses and entire neurons. Normal gray matter development includes a peak in volume representing this shift, which is region specific and follows a set course from primary sensory and motoric regions to more complex regions and ending in the prefrontal cortex (Shaw et al. 2008). Contrary to this, white matter volume normally increases due to ongoing myelination, especially of long-range fibers, well into the late 20s (Gibson 1991). Both normal developments are threatened by the lack in nourishment due to AN, especially, as new white matter fibers and those still under development have been proven to be most susceptible to insults (Gibson 1991).

Hormonal changes mentioned above may also play a significant role in these volume alterations. Increased cortisol levels, for example, are known to lead to brain atrophy (Chen et al. 2020) and have indeed been associated with brain volume

reduction in AN, together with lack of trophic thyroid hormones (Castro-Fornieles et al. 2010; Chui et al. 2008; Nogal et al. 2008). Also reduced leptin and brain-derived neurotrophic growth factor (BDNF) could have an effect on brain volume changes (Holtkamp et al. 2006). Trophic gonadal hormones appear to play an important role in brain volume changes during healthy development (Neufang et al. 2009) and in AN. They have been shown to be associated with sulcal width, a proxy for brain volume reduction (Nogal et al. 2008), while our own group could show follicle stimulating hormone (FSH) to be correlated with brain volume increase following short-term weight recovery (Mainz et al. 2012). Chui et al. (2008) showed persisting amenorrhea and ensuing lack of estrogen to be the most important contributor to still decrease cognitive function in otherwise recovered patients with AN (Chui et al. 2008).

The cellular underpinnings of these volume changes remained largely unclear until recently, mostly due to the lack of postmortem analyses of deceased patients with AN. Two historic papers report a total of three analyses with signs of neuronal degeneration and altered dendritic spine morphology and ramification patterns in gray matter (Martin 1958; Neumarker 1997). Recently, animal models have been used to study the underlying cellular changes associated with this important, yet until then, elusive phenomenon of these significant brain volume reductions. The most common animal model used is the so-called activity-based anorexia (ABA) model in rodents (Frintrop et al. 2018; Routtenberg and Kuznesof 1967). Reduced food availability is coupled with running wheel access and induces a seemingly contra-intuitive increase in running wheel activity in susceptible animals, leading to further increased weight loss and even death. Food-seeking behavior by rodents is named as a possible explanation for this increased physical activity (Kas and Adan 2011), behaviorally matching the hyperactivity often seen in patients with AN. Most somatic changes experienced by patients can be studied using this animal model including reduced food intake, weight reduction, drop in body temperature, hyperactivity, amenorrhea, hypoleptinemia, and hyperghrelinemia (Frintrop et al. 2018). Our own analysis could for the first time reproduce the brain volume loss seen in patients with AN in both gray and white matter, further validating the model for the study of brain alterations. We could even show (almost) complete volume recovery after weight rehabilitation – only white matter volumes did not recover fully, potentially hinting at some enduring and longer-lasting effects (Frintrop et al. 2017; Frintrop et al. 2019). Cellular analyses of neurons by the group of Aoki et al. (2014) revealed increased GABA receptors in hippocampal neurons, especially in spines that were possibly associated with increased tonic inhibition and anxiety, further increasing hyperactivity and weight loss (Aoki et al. 2014). When investigating neuronal cell death or shrinkage as underlying mechanisms for brain volume reduction, our own analysis, however, showed a normal neuronal cell count and normal general neuronal cell sizes in ABA animals (Frintrop et al. 2017). This fits well with clinical data as extensive neuronal cell death as cause of the remarkable volume reductions would appear unlikely, as most of the volume is regained upon weight recovery – however, neurons are not known to regrow once dead.

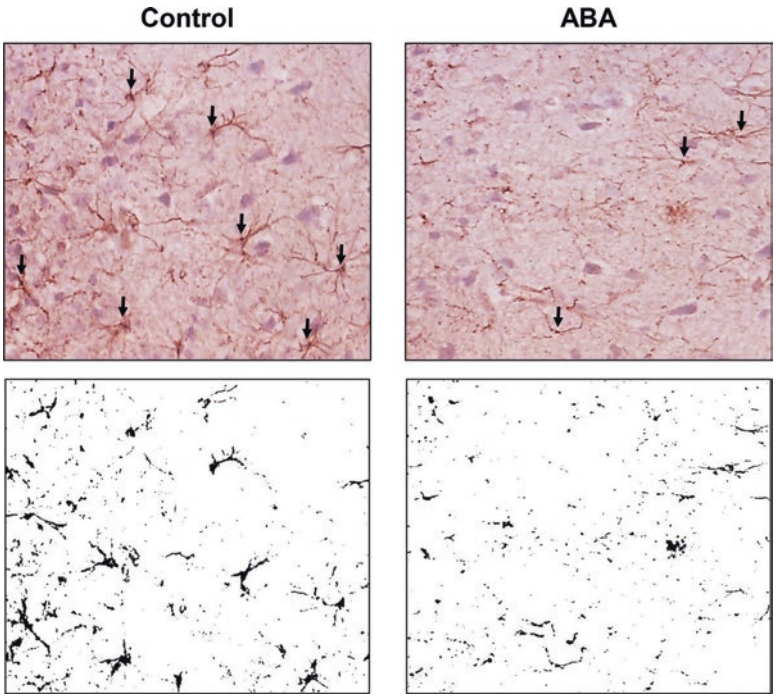

Fig. 2 Astrocyte counts in the rat cortex. Control animals (left); ABA animals after 3 weeks of semi-starvation and running wheel access (right). Upper panel GFAP immunostaining, lower panel, surface measurement using densitometry. Note the reduction of astrocyte numbers of about 50% and the even more pronounced reduction in surface area occupied by astrocytes

Conversely, significant reductions in cell numbers were found in GFAP$^+$ astrocytes by our group and others (Banasr et al. 2011; Frintrop et al. 2017, 2018; Reyes-Haro et al. 2015) (see Fig. 2).

Reyes-Haro et al. (2016) used a different animal model (Reyes-Haro et al. 2016). They used the effect of dehydration that leads to reduced hunger, diminished feeding, and weight loss and found slightly reduced numbers of astrocytes in the hippocampus and corpus callosum (Reyes-Haro et al. 2015; Reyes-Haro et al. 2016). Our own group could greatly expand these findings by using a chronic starvation model with a total of 3 weeks of (controlled) reduced feeding leading to a roughly 50% reduction in astrocyte cell count and even up to 90% reduction in astrocyte cell surface indicating fewer and smaller cell bodies. Our findings were corroborated with a second measurement approach by an over 50% reduction in mRNA expression of GFAP. By assessing brain volume changes and astrocytes in the same sample, we were furthermore able to uncover a direct link between decreased astrocyte cell count and volume reduction for the first time (Frintrop et al. 2017). Interestingly, these findings were not found in an acute model following only 1 week of starvation, underlining the importance of prolonged and cumulative starvation effects on the brain and its cells. Furthermore, neither neurons nor oligodendrocytes showed

similar reductions, making this cell count and size reduction specific to astrocytes (Frintrop et al. 2018). In a separate study, we could replicate these findings and additionally show a complete recovery of astrocyte cell count, cell volume, and GFAP mRNA expression upon 2 weeks of refeeding, emphasizing the general reversibility of these findings, well in line with the largely reversibility of brain volume reductions (Frintrop et al. 2019). However, more research is needed with even longer periods of starvation in the animal model to study the equivalent of long and enduring AN (>3 years) with even more pronounced neuroanatomical and neuropsychological consequences in patients.

The Origin of Astrocyte Loss in AN

As astrocytes are subject to an active turnover of neogenesis and apoptosis, two potential mechanisms explaining astrocyte loss come into mind: reduced neogenesis or increased apoptosis. Here, Barbarich-Marsteller et al. (2013) showed glia cell proliferation indeed to be reduced in the dentate gyrus, dorsal hippocampus, and corpus callosum (but not in known regions with neurogenesis like the subgranular zone of the dentate gyrus) using Ki67 and BrdU staining in ABA animals (Barbarich-Marsteller et al. 2013). We could extend these findings and simultaneously analyze Ki67 as proliferation marker and Caspase 3 as apoptosis marker in the same sample described above. We found a significant reduction of neogenesis of about 50% while not evidencing any increase in apoptosis. This fits well with the catabolic state occurring during semi-starvation, where there is not enough energy to build the same amount of new astrocytes (Frintrop et al. 2019).

Potential Functional Consequences of Astrocyte Loss

Such a dramatic reduction in astrocyte cell count could have severe implications for astrocyte functioning. As astrocytes play an active role in constituting the blood-brain barrier, transporting nutrients and blood-based messengers into the brain, alimenting neurons, neurotransmitter reuptake, as well as in synapse formation and plasticity (Kaczor et al. 2015; Molofsky et al. 2012; Panatier and Robitaille 2012), their reduction by half can be hypothesized to interfere with these tasks. Astrocytes have been associated with complex phenomena such as mood and sleep – the first covered in detail in previous chapters of this book. In brief, astrocytes are reduced in numbers in patients with depression, and artificially reducing astrocytes in the frontal cortex leads to symptoms of depression in animal models (Fellin et al. 2012). Reduced numbers of astrocytes in AN could help explain concurrent symptoms of depression, sleep disturbances, and learning impairments often seen in patients with AN (Buhren et al. 2014). In our own lab, we could show learning impairments in the novel object recognition task in ABA animals, which was further linked to estrogen

reduction (Paulukat et al. 2016). Altered synapse formation and neuronal plasticity due to reduced astrocytes could also help explain the increased rigidity of our patients and their decreased cognitive flexibility with increased attention to details. As patients with AN also typically display a lack of insight into the illness and a low motivation of change, these impaired learning processes and flexibility could help understand difficulties in the cognitive processes involved in psychotherapy of patients during starvation and partially explain why psychotherapy in acutely ill patients is unsuccessful. Following chronic starvation, long-lasting metabolic deprivation and astrocyte loss could help explain the behavioral neurodegenerative symptoms described above (Treasure et al. 2015). This hypothesis is further strengthened by volumetric studies showing further worsening brain volume loss in these patients with increasing illness duration.

Astroglia as Targets for Gonadal Steroid Hormones

By which mechanisms can astrocytes be influenced during semi-starvation in AN and which consequences could be expected on a cellular level? Detailed research in this field is still scarce; however, we here summarize the state of the literature and present first findings with special regard to the altered metabolic and endocrine situation of patients with AN including the chronic lack of gonadal steroid hormones, since changes in steroid synthesis, availability, and cellular signaling are well described in AN (Schorr and Miller 2017; Støving et al. 1999).

Historically, astrocytes are regarded as support cells for neurons. Research data of the past decades, however, have demonstrated a large variety of functions in the brain such as the regulation of endothelial cells and contribution to the blood-brain barrier (BBB), neurotransmitter metabolism and recycling, provision of nutrients and extracellular ion balance, synapse shielding, and others (Kimelberg and Nedergaard 2010). After CNS damage or chronic neuropathological processes, astrocytes may develop into a reactive phenotype, often referred to as A1 type, with changes in morphology and function. Astrogliosis and scar formation are typical characteristics of such pathologies (Sofroniew 2009). More recent research data additionally highlight that activated astrocytes are becoming part of the local brain-intrinsic inflammatory system (including microglia, nearby neurons, and endothelial cells) after damage and provide an array of pro-inflammatory cytokines and chemokines which regulate neighboring cells and infiltrated peripheral immune cells (Cekanaviciute and Buckwalter 2016; Johann and Beyer 2013; Scheld et al. 2016). Furthermore, we have shown that astrocytes are key sensors of and important for the surveillance of local oxidative stress phenomena and elimination of oxidants through the nuclear factor-erythroid 2 p45-related factor 2 (Nrf2)/antioxidant response element (ARE) system (Draheim et al. 2016). And finally, activated astrocytes are able to monitor and induce pyroptosis, i.e., an inflammatory form of lytic-programmed cell death. To execute this physiological response, they are equipped with several components of the intracellular multi-protein inflammasome complex

which enables glia to respond to damaging stimuli in the brain and thereby produce temporarily large quantities of interkeukin-1β (IL1β) (Heitzer et al. 2017; Mortezaee et al. 2018; Slowik et al. 2018). These data altogether highlight the importance of astrocytes for proper brain functionality but also stress the issue that they are an integral component of the regulation of acute and chronic neuropathological processes.

The multitude of functions and roles in the CNS make astroglia a primary objective for well-balanced regulation and, in the case of brain-threatening events, therapeutic interventions.

As mentioned in the introduction, AN is generally associated with a number of profound endocrine alterations at different individual magnitudes. To date, it is not clear which of these AN-related changes are reactive, adaptive, or etiologic. Irrespectively, this part will discuss some aspects of steroid hormone-astroglia interactions and start with the role of gonadal steroids, i.e., estrogens and progestins. Intriguing observations in AN patients are that this disease shows a clear gender bias and is predominantly apparent in young women and that there occurs an early disturbance or even loss of the menstrual cycle and associated therewith a massive reduction of blood gonadal steroids (Young 2010). It was suggested by these authors and others that abnormal responses to estrogens may be due to an altered responsiveness of brain cells and functional abnormalities. This phenomenon might result from genetic polymorphisms in genes coding for classical nuclear estrogen receptors (nER) and membrane-associated ERs (mER). Such a disturbed estrogen signaling could be the reason for the insufficient feedback regulation during the estrous cycle in AN patients and thus account for amenorrhea (Ramoz et al. 2013). Similar observations although less detailed were reported for progesterone synthesis and signaling and functional aspects of the specific nuclear or membrane-bound progesterone receptors (nPRs, mPRs) (Klump et al. 2013; Singhal et al. 2014). What can be the connection between astrocytes and the above findings? First, rodent astrocytes cultured under starvation conditions, i.e., "hungry astrocytes," reveal a so-called A1 activation state with an unfolded protein response consisting of an accumulation of misfolded proteins in the endoplasmic reticulum ((Kogel et al. 2021) see also below). This pathophysiological condition reflects increased and unbalanced cellular oxidative stress and has been described to play a role in the development of metabolic diseases like obesity and diabetes (Yang et al. 2017). Second, astrocytes express receptors for appetite-promoting factors such as ghrelin (Frago and Chowen 2017) and are part of the brain inflammatory system which is implicated in the development of obesity and related disorders (Seong et al. 2019). Third, astroglial cells in different brain regions express the complete battery of nER/mER and nPRs/mPR, although there exist variations in expression levels depending on the developmental stage, aging, and gender but also in brain disorders and neuropathological events (Azcoitia et al. 2010; Brotfain et al. 2016; Habib et al. 2014; Johann and Beyer 2013; Karki et al. 2014; Pawlak et al. 2005a; Pawlak et al. 2005b).

How can estrogen signaling in astrocytes interfere with the manifestation or reinforcement of AN? It is well-known that ERs interact with insulin-like growth factor-1 (IGF-1) receptors in the CNS to regulate neural functions (Mendez et al. 2006).

This is of particular interest, since there exists a clear correlation between IGF-1 levels, the dysregulation of the growth hormone-IGF-1 axis, the psychopathology of AN, and related eating disorders (Brambilla et al. 2018; Fazeli and Klibanski 2012). Ghrelin, an important gut-brain axis peptide, promotes food intake, and estrogen upregulates ghrelin levels in different organ systems as shown by the use of estrogen-deficient animal experiments (Matsubara et al. 2004; Wang et al. 2015). Astrocytes are reported to be versatile metabolic sensors for the maintenance of CNS homeostasis and represent ghrelin targets (Marina et al. 2018). This might explain the role of astrocytes in mediating central effects of ghrelin on food intake (Frago and Chowen 2017). Hypothalamic astrocytes also express leptin receptors and thereby regulate hypothalamic neurons and neural circuits involved in food intake (Kim et al. 2014). Astroglia-specific leptin receptor activation caused an increased food intake after ghrelin administration (Kim et al. 2014). Despite the abovementioned evidence, no adequate literature information is available on the ghrelin/leptin system in astrocytes in human AN patients or in respective animal models.

These data convincingly point at a setscrew role for astrocytes in the brain-intrinsic control of eating, at least in the hypothalamus. Astroglial end feet surround the CNS vasculature and represent an important part of the BBB. Thus, astrocytes are ideally placed at the interface between the peripheral vascular system and the brain to sense metabolic changes and endocrine signals. BBB astrocytes on the other side possess finely branched extensions wrapping synapses and contacting nearby neurons. From a functional point of view, these specifically located astroglial cells express glutamate receptors, ion and water channels, and selective membrane transporters (reviewed by Marina et al. (2018)) which allow them to selectively tune synaptic transmission and neural communication. Particularly, the presence of the water channel protein aquaporin-4 allows astrocytes to rapidly respond to external signals and generate brain volume fluctuations (Noell et al. 2007) similar to those observed in the ABA rat model (Frintrop et al. 2017; Frintrop et al. 2019) and in human AN patients (Seitz et al. 2018). It is of interest that estrogens affect the expression and activation of aquaporin-4 water channels in astrocytes und pathological conditions (Habib et al. 2014). Thus, estrogen deficiency as observed in AN could diminish water efflux/influx and equilibrium in the brain and affect ion homeostasis by targeting astrocytes.

Patients with AN develop multiple endocrine abnormalities including a disturbance of the hypothalamus-pituitary-adrenal axis with particular changes in the activity of the growth hormone (GH)/IGF-I axis (Gianotti et al. 2002). Other lines of evidence suggest that neurotrophins and in particular brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) alterations are implicated in the etiology of eating disorders and therefore could be used as biomarkers for AN (Dmitrzak-Weglarz et al. 2013; Ribasés et al. 2003). Hypothalamic astrocytes not only are targets for BDNF but also synthesize BDNF thereby influencing neuronal activity (Caruso et al. 2012). BDNF synthesis by astrocytes is regulated by estrogens which allows this steroid hormone to promote neural networks under physiological conditions but coincidently fulfill a neuroprotective role in the brain after injuries (Sohrabji and Lewis 2006). Similarly,

astrocytes in the hypothalamus express GDNF which is under the control of estrogen signaling (Ivanova et al. 2002). Both gonadal steroid hormones dampen central and brain-intrinsic immune responses and regulate local growth factor supply mediated by astrocytes. This complex modulation requires the gamut of steroid-dependent signaling pathways (Kipp et al. 2012). The identification of molecular and cellular targets of sex steroids and the understanding of cell-cell interactions in the pathogenesis of AN will offer promise of novel therapy strategies generally during brain pathologies but particularly also for AN.

Another intriguing aspect of astrocyte function is the removal and recycling of the neurotransmitter glutamate. Therefore, astrocytes express highly specific glutamate transporters which belong to the family of membrane-bound excitatory amino acid transporters (EAAT). Astroglial glutamate-aspartate transporter (GLAST, EAAT1 as human homolog) and glutamate transporter-1 (GLT-1, EAAT2 as human homolog) are the major transporters which take up synaptic glutamate from the synaptic cleft to maintain physiological extracellular glutamic levels, thus preventing extracellular glutamate accumulation and ensuing excitotoxicity (Mahmoud et al. 2019). GLT-1 is responsible for over 90% of glutamate reuptake within the CNS, typically found in astrocytes but only marginally in neurons. The dysregulation of GLAST/GLT-1 plays a significant role in excitotoxicity and is associated with the neuropathogenesis of other psychiatric diseases (Pajarillo et al. 2019), also described in this book. There is no direct information in the literature available associating glutamate transporters and its dysfunction with AN. However, there exist experimental data and information from human studies concerning abnormal glutamate levels in AN patients. Widespread reductions in brain glutamate concentrations were measured using high-field magnetic resonance (MRS, 7 T) imaging in women with AN (Godlewska et al. 2017). Another study identified distinct hypothalamic neurochemical dysfunctions, i.e., paradoxical glutamate reductions, and associated structural variations in hypothalamic nuclei implicated in food intake and energy balance (Florent et al. 2020). Interestingly, the regulation of the glutamate transporters GLAST and GLT-1 is highly influenced and controlled by circulating estrogens particularly in astrocytes (Pawlak et al. 2005a), whereas in neurons, estrogens selectively interfere mainly with the regulation of vesicular glutamate transporters responsible for storage and release (Mela et al. 2016). When considering this information about the glutamate-astroglia-hypothalamus-estrogen connection, it becomes evident that pathophysiological disturbances of the glutamatergic system as observed in AN may strongly contribute to the maintenance of the disease state and go hand in hand with abnormal plasma estrogen levels (Hermens et al. 2020).

Finally, we would like draw particular attention to the mitochondrial compartment of astrocytes, its involvement in AN pathology, and possible regulation by gonadal steroid hormones. Alterations of hypothalamic proteins involved in energy and mitochondrial metabolism have been observed in ABA mice where mitochondrial dynamics in the hypothalamus appear to be modified with an increase of fission without modification of fusion (Nobis et al. 2018). Hypothalamic mitochondrial respiration and uncoupling protein 2 are all described downstream targets mediating the orexigenic effects of ghrelin (Lim et al. 2011). Atypical levels of ghrelin are

clearly associated with metabolic conditions such as obesity and AN. With respect to the respiratory chain components, female AN patients revealed increased activities of complexes I and II in isolated platelets (Böhm et al. 2007). Further, the mitochondrial membrane potential seems to be decreased and reactive oxygen species (ROS) production elevated in leukocytes from anorexic patients pointing at an increased oxidative stress status at the level of complex I (Victor et al. 2014). There is convincing evidence that estrogens interfere with mitochondrial functioning and that the estrogen-mediated control of the mitochondrial compartment involves the cooperation of nERs/mERs and their co-activators on the coordinate regulation of genes for respiratory chain complex proteins (Chen et al. 2009). We have previously reported that estrogen influences the gene expression of respiratory chain proteins in astrocytes of the rodent cerebral cortex (Araújo et al. 2008). Apparently, this regulation occurs in a gender-specific way suggesting male/female differences in the protection against vulnerability and adaptive capacity of the mitochondria to external pathological stimuli (Arnold et al. 2008). Thus, the mitochondrial system seems to be regulated by estrogens at the level of ATP and ROS production as well as under a structural-functional viewpoint. This implies that sex steroids can directly and indirectly interfere with mitochondrial properties via non-nuclear, presumably mitochondria-intrinsic, and nuclear signaling mechanisms. This enables this cell organelle to cope with pathological processes and provide stabile local energy homeostasis and an anti-apoptotic base setting in the brain.

Taking into account that estrogen levels are massively reduced in AN similarly to AN-related animal models, physiological parameters such as glutamate homeostasis, mitochondrial performance, ROS elimination, water fluctuations, and growth factor supply by hypothalamic astrocytes are all imbalanced up to completely dysregulated. This, in consequence, may have strong negative effects on the function of neural circuits embedded in food intake and energy balance and thus contribute to either the development of AN or the perpetuation of this eating disease. Detailed research into these functional consequences of gonadal steroid suppression and astrocyte reduction in AN is thus highly promising to help further unravel underlying pathophysiology.

Inflammation in AN and the Role of Astrocytes

We already undertook the task of studying astrocyte function under semi-starvation conditions by creating a cell culture setup of chronic starvation. This work focused mostly on inflammation properties of astrocytes, as they play a prominent role in immune regulation, inflammation, and its attenuation, while a chronic low-grade state of inflammation has been found in patients with AN in large meta-analyses, which remains poorly understood (Dalton et al. 2018; Solmi et al. 2015).

Inflammation in AN

First reports of inflammatory reactions in patients suffering from AN date back in the early 1990s. It has been known at least since 1992 that the pro-inflammatory marker TNFα is expressed at mildly elevated levels in the blood of patients with AN (Schattner et al. 1992). In addition, other studies showed moderately increased expression of other pro-inflammatory cytokines such as IL6 and IL1β or associated receptors (Misra et al. 2006; Nakai et al. 2000; Ostrowska et al. 2015). Although some studies were not able to find changes in cytokine expression between patients with AN and healthy control subjects (Brambilla et al. 2001), the increased cytokine expression has been confirmed several times over the years and has even been associated with a predisposition to develop AN (Agnello et al. 2012; Kanbur et al. 2008). In order to give a better overview of the expression of pro-inflammatory markers in patients with AN, two large meta-analyses were performed. Both studies described an elevated concentration of IL6 and TNFα in the blood of patients with AN (Dalton et al. 2018; Solmi et al. 2015). Solmi et al. (2015) additionally found an increase in IL1β concentration which was confirmed by Dalton et al. (2018) only for the restrictive subtype of AN. However, a common feature shared by all these studies is the increased expression of pro-inflammatory markers, which is the reason why a low-grade inflammatory state during AN can be assumed. This assumption is corroborated by the fact that parameters of inflammation are increasingly expressed in peripheral blood mononuclear cells (PBMCs). In PBMCs of patients with AN, increased expression of COX2 as well as phosphorylation of p38 MAPK and p-ERK points toward a stress response of these cells in combination with an inflammation (Caso et al. 2020). COX2 is activated by cytokines during inflammation and injuries. It is involved in the production of prostaglandins that can promote inflammation and mediate pain (Simon 1999). p38 MAPK and p-ERK are part of the MAPK pathway which is activated by extracellular stress stimuli like ultraviolet light, heat shock, and pro-inflammatory cytokines. The MAPK pathway seems to play a major role in apoptosis and cell senescence but also in cell proliferation (Obata et al. 2000; Zou et al. 2019). The concomitant low expression of NFκB, a transcription factor involved in inflammation, and the increased level of the anti-inflammatory cortisol and glucocorticoid receptors, further indicates an altered regulation of inflammatory signaling pathway in patients with AN (Caso et al. 2020; Luz Neto et al. 2019). In view of the previously described results, it can be said that there is strong evidence of a low-grade inflammatory response in AN. This inflammatory reaction is, however, mostly reversible. It has been shown that altered cytokine concentrations normalize after body weight rehabilitation (Allende et al. 1998; Pomeroy et al. 1994; Schattner et al. 1990; Solmi et al. 2015). In a recent longitudinal study of cytokine concentrations, a decrease of IL6 levels after 12 weeks was correlated with improved eating disorder symptoms. For this reason, IL6 may be considered as a biomarker to assess severity of AN in the future (Dalton et al. 2020).

Astrocytes and Inflammation in the CNS

Astrocyte function includes a response following injury of the central nervous system (Sofroniew and Vinters 2010). Brain injuries and neurological diseases are able to shift astrocytes into a so-called reactive state which results in astrogliosis (Liddelow and Barres 2017). Reactive astrocytes undergo multiple changes at the molecular, cellular, and functional level (Sun and Jakobs 2012).

At the molecular level, translocation of the nuclear factor ƙ-lightchain-enhancer of activated B cells (NFƙB) in the nucleus initiates the activation of astrocytes. This translocation can be caused by pro-inflammatory stimuli (Brambilla et al. 2005; Dorrington and Fraser 2019). These include, for example, tumor necrosis factor α (TNFα), interleukin 1β (IL1β), and interleukin 17 (IL17) (Hyvärinen et al. 2019; Qian et al. 2007), reactive oxygen species (ROS) (Chandel et al. 2000), phagocytosed myelin (Ponath et al. 2016), and toll-like receptor (TLR) engagement (Kawai and Akira 2007). The increased expression of glial fibrillary acidic protein (GFAP) is a prominent marker for reactivity of astrocytes (Yang and Wang 2015). Other markers associated with astrocyte activation are, for example, pro-inflammatory cytokines (IL1β, IL6, IL8, TNFα, and granulocyte-macrophage colony-stimulating factor (GM-CSF)) as well as chemokines (CC-chemokine ligand 3 (CCL3), CCL5, and C-X-C-motif chemokine ligand 10 (CXCL10)) (Choi et al. 2014). During inflammation, a bidirectional communication between astrocytes and microglia influences the inflammatory process (Matejuk and Ransohoff 2020). Microglia secrete IL1α, IL1β, and TNFα to activate a transcriptional response in astrocytes leading to an increase in neurotoxic and a decrease in neurotrophic factors (Liddelow and Barres 2017), whereas astrocytes promote microglial inflammation through the production of IL6, GM-CSF, and other signaling factors (Linnerbauer et al. 2020).

On a functional level, astrocyte reactivity and astrogliosis are originally protective responses. They are designed to ward off acute stress, to minimize tissue damage, and to restore brain homeostasis (Sidoryk-Wegrzynowicz et al. 2011) These functions can be achieved by glutamate uptake, removal of free radicals, production of neurotrophins, and scar formation which restricts the damage to a limited area (Chen and Swanson 2003). However, under certain circumstances, reactive astrocytes promote neurotoxicity (Liddelow and Barres 2017). In this context, reactive astrocytes can be differentiated into at least two phenotypes (Liddelow et al. 2017; Zamanian et al. 2012). A1-like astrocytes appear pro-inflammatory and promote neurotoxicity. They are activated by microglia releasing cytokines and the following NFƙB activation (Liddelow et al. 2017). These astrocytes loose many of their main functions including their ability to promote neuronal survival leading to toxicity for neurons and oligodendrocytes, as well as showing a decreased ability to support synapse formation and function which could lead to an impaired learning behavior (Liddelow and Barres 2017). Neurotoxicity is promoted in several ways, for example, by decreasing their expression of glutamate transporters. The result is a deficient control of neurotransmitter uptake and release (Landeghem et al. 2006). Furthermore, NFƙB signaling in astrocytes during CNS inflammation leads to an

excessive production of NO and brain-derived neurotrophic factor (BDNF) (Hsiao et al. 2013; Kaltschmidt and Kaltschmidt 2015). In the healthy brain, BDNF promotes neuronal survival (Kowiański et al. 2018). Excessive levels of BDNF, however, result in NO production and neuronal cell death (Colombo et al. 2012). An A2-like astrocyte, on the other hand, is neuroprotective, upregulates neurotrophic genes, and promotes neuronal survival. (Liddelow and Barres 2017).

Astrocytes and Metabolic Diseases

Besides an immune response in the brain, astrocytes are also responsible for metabolic support of neurons. Neurons have one of the highest requirements of glucose of all cells in the whole body (Mergenthaler et al. 2013). By metabolizing lactate from glycogen, astrocytes provide energy to neurons in times of an undersupply. This way, astrocytes thus ensure the survival and function of neurons (Kasischke et al. 2004; Pellerin and Magistretti 1994). For this reason, it is not surprising that the involvement of astrocytes in metabolic diseases, such as obesity and diabetes, has already been demonstrated. For example, increased astro- and microgliosis in the hypothalamus have been linked to development and maintenance of obesity (Rahman et al. 2018). A relationship between other diseases with metabolic aspects such as anorexia nervosa (AN), neuroinflammation, and associated activation of astrocytes remains unclear.

The *Hungry* Astrocyte In Vitro

In order to determine the importance of astrocytes in the event of nutrient deficiency, our group aimed to established a cell culture model. Due to chronic nutritional deficiencies over many years (Nagl et al. 2016), patients with AN often suffer from mild hypoglycemia, which is usually asymptomatic (Levenson 2011; Mattingly and Bhanji 1995). In order to simulate this situation as accurately as possible, we supplied astrocytes in vitro with a glucose concentration just below the physiological level of the brain at 2.4 ± 0.1 mM (Kogel et al. 2021). To represent the extended course of disease as it occurs during AN, in our study, astrocytes were chronically semi-starved over 15 days (Kogel et al. 2021). This differs from previous glucose deprivation studies that use acute starvation ranging from 30 min to 48 h (Hara et al. 1989; Lee et al. 2016; Pauwels et al. 1985). Treating cells with a glucose concentration of 2 mM for at least 2 weeks is expected to induce chronic undernutrition but not massive cell death. Both assumptions were previously shown by an in vitro study performed by Abe et al. (2006) and confirmed by our data. After 3 weeks of supplying astrocytes with a glucose concentration of 2 mM, their starved cells showed an empty glycogen store and an altered metabolism (Abe et al. 2006). Astrocytes are able to store small amounts of glycogen and metabolize them via

glucose to lactate in case of metabolic undersupply (Falkowska et al. 2015). In this way, the energy supply of neurons can be maintained despite an acute deficiency (Kasischke et al. 2004). Therefore, an empty glycogen store in astrocytes of the CNS is an indication of prolonged starvation. Our group could demonstrate further indications of an altered supply situation after treatment of astrocytes with 2 mM glucose over 15 days. This involved a reduced expression of connexin43 (Cx43) in chronically semi-starved astrocytes in vitro (Kogel et al. 2021). The transport of glucose and other small molecules occurs within the astrocytic network via the gap junctions (Allard et al. 2014), which in astrocytes of the CNS are mainly composed of Cx43 (Nagy and Rash 2000). Reduced expression of this component impedes the supply of neurons, since rapid distribution of lactate is no longer guaranteed (Mayorquin et al. 2018). In the same in vitro study, we did not find increased cytotoxicity or impaired general metabolic activity after semi-starvation of astrocytes for 15 days (Kogel et al. 2021) although semi-starved astrocytes switch their metabolism to lactate and glucose oxidation (Abe et al. 2006). However, our semi-starved astrocytes in vitro did show an increased inflammatory reaction. In our study, astrocytes starved for 15 days expressed a change in morphology resulting in hypertrophy of soma and processes (Kogel et al. 2021) (see Fig. 3), indicating increased reactivity (Li et al. 2019). Furthermore, we could demonstrate an upregulated expression of pro-inflammatory cytokines such as IL6 in these astrocytes indicating an inflammatory response. Increased expression of A1 markers, for example, C3 and Psmb8, with concomitant decrease of A2 markers (e.g., S100a10) in the same study indicates a phenotype switch to a pro-inflammatory and harmful phenotype (Kogel et al. 2021). All these reactions point toward an inflammatory reaction, accompanied by reactivity and astrogliosis in chronically semi-starved astrocytes.

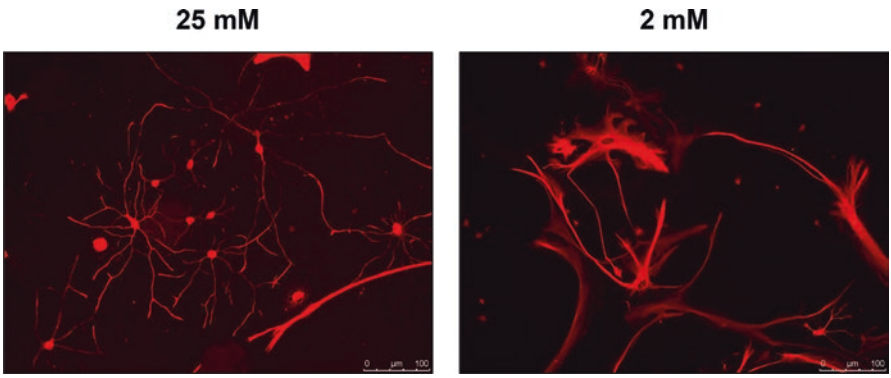

Fig. 3 Cell morphology of primary rat astrocytes cultured in glucose control medium (25 mM) (left) or after 15 days of chronic semi-starvation (2 mM) (right) indicated by an immunofluorescence staining with GFAP. Note the "activated" morphology of the semi-starved astrocytes with hypertrophy of cell bodies and reduced branching

Astrocytes in Animal Models of AN

Using the dehydration animal model of AN, Reyes-Haro et al. (2016) were able to demonstrate morphological changes in hippocampal astrocytes which also point toward an astrocyte activation. This assumption is supported by an increased expression of vimentin and nestin in the hippocampus of the same animals, indicating an elevated number of reactive astrocytes (Reyes-Haro et al. 2016). Simultaneously, increased expressions of IL6 and IL1β demonstrate an inflammatory response in the hippocampus of the same animal model (Ragu-Varman et al. 2019). This inflammatory response in the brain may be mediated by an increased level of T-lymphocyte receptors 4 (TLR4) in intestinal epithelial cells and intestinal macrophages (Belmonte et al. 2016). TLRs are able to trigger an inflammatory response (Moresco et al. 2011). Increased expression of TLR4 was found in the gut of ABA animals and associated with elevated levels of IL1β and its receptor in the hypothalamus. In addition, TLR4-deficient mice are more susceptible to the effects of the ABA model and lose weight faster than non-deficient mice (Belmonte et al. 2016). This suggests that the inflammatory response triggered by TLR4 could also in part represent a form of a protective mechanism.

In summary, AN is associated with increased inflammatory reactions and an altered function of inflammatory pathways. The extent to which this inflammation is associated with brain volume loss, found in patients with AN and decreased numbers of astrocytes observed in the ABA animal model, requires further investigation.

Gut Microbiota Alterations in AN and the Influence on Astrocytes

A rather new aspect in AN research refers to the interaction with gut microbiota and the gut-brain axis with clear implications for brain morphology including cellular and functional changes in the brain and behavioral consequences like affected learning, mood, anxiety, eating behavior, and weight gain (Seitz et al. 2019).

The Microbiome: General

The gastrointestinal tract of every human being is colonized by approximately 1–2 kg of bacterial cells collectively referred to as gut microbiota. The number of gut microbiota is at least as large as the number of eukaryotic cells in the organism (Sender and Fuchs 2016; Sgritta et al. 2019). The colonization with gut bacteria mainly takes place with birth and reaches a steady state in early childhood. Every individual hosts roughly 500 different species out of about 2000 so that a unique

composition is created (Almeida et al. 2019; Arumugam et al. 2011). This composition can shift throughout life and is influenced by various factors such as birth mode, genetics, environment, and diet (Ananthakrishnan 2015; Marques et al. 2010). The colony of gut microbiota interacts with the host in a symbiotic manner by breaking down food and providing the host with energy and essential nutrients that otherwise would not be available. Moreover, the gut microbiota plays a relevant role in the development of the immune system, inflammatory processes, and regulation of appetite and body weight (Fetissov 2017; Neuman et al. 2015; Ridaura et al. 2013). Due to these manifold functions, a dysbiosis in the microbiota population, which means alterations in the species diversity and taxonomic composition, can lead to a disruption of the host's homeostasis. Initially, gastrointestinal disorders such as inflammatory bowel disease, ulcerative colitis, and allergies (e.g., celiac disease) were associated with changes in the gut microbiota (Gigante et al. 2011; Noor et al. 2010; Subramanian et al. 2006). Later, a wide range of other diseases were suggested to be affected by microbiota imbalances, among others Alzheimer's disease, multiple sclerosis, cancer, and psychiatric conditions (Cryan and Dinan 2012; Jiang et al. 2017; Mangiola et al. 2016). In the last years, evidence is growing that gut microbiota also influence mood and behavior as observed in people with mood disorders (e.g., major depression disorder and bipolar disorder) (Cryan and Dinan 2012; Huang et al. 2019; Kelly et al. 2017). It appears obvious that gut microbiota alterations might play a role in the pathophysiology of anorexia nervosa (AN) because relevant processes such as body weight and appetite regulation and metabolic and immunological processes were shown to be influenced by gut microbiota and depression represents a common comorbidity (Asano et al. 2012; Fetissov 2017; Morkl et al. 2017; Ridaura et al. 2013). However, it is often not clear whether the different bacterial composition contributes to the cause of the disease or rather represents an effect of the disorder.

In order to explain the interplay between gut microbiota and psychiatric disorders, the so-called gut-(microbiota)-brain axis needs to be considered (Rhee et al. 2009). A lot of gut bacteria produce or modulate specific metabolites and are again affected by them, e.g., short-chain fatty acids, neurotransmitters (e.g., dopamine, norepinephrine, and serotonin), and hormones (e.g., ghrelin, leptin, and glucagon-like peptide-1) in the gastrointestinal tract. Additionally, some of the mentioned effectors can execute a bidirectional signaling pathway to the brain and vice versa as part of the gut-brain axis (Clarke et al. 2014; Rhee et al. 2009). Some effector molecules are translocalized from the gut lumen into the systemic blood circulation and thereby possibly transported to the brain to transmit a signal (Ticinesi et al. 2019). Another way of gut-brain communication takes place via the vagal nerve that connects the brainstem to many organs including the gastrointestinal tract (Breit et al. 2018) and has been found to modulate gut-brain interaction (Sgritta et al. 2019).

Recently, Hata and colleagues showed that transplantation of gut bacteria populations isolated from patients with AN into germ-free mice that were born and raised under sterile conditions indeed led to reduced food intake and body weight in their offspring. Moreover, a lower food efficiency ratio defined as body weight gain per food intake was recorded in the offspring compared to controls (Hata et al. 2019).

In addition, anxiety-like behavior and compulsive behavior assessed by the open field and marble-burying tests, respectively, also common comorbidities in AN, were increased in the offspring of mice that received the fecal microbiota transplantation from patients with AN (Hata et al. 2019). These results showed for the first time a causal effect of gut microbiota on appetite and bodyweight regulation and behavioral alterations in an animal model. Similarly, changes in phenotypes after fecal microbiota transplantation can be observed with regard to other disorders such as depression and obesity (Kleiman et al. 2015; Ridaura et al. 2013).

The Microbiome: Anorexia Nervosa Animal Model

Comparable to studies in patients with AN, clear differences in the gut microbiota composition between food-restricted animals and normally fed controls were observed in studies using the activity-based anorexia (ABA) model (Breton et al. 2020; Queipo-Ortuno et al. 2013; Trinh et al. 2021).

As described before, the ABA paradigm is a translational animal model to mimic symptoms of AN using a combination of food reduction and access to a running wheel (see above). We used a chronic version of the ABA model (Frintrop et al. 2018) with separate control groups for food reduction and running wheel access and showed that food reduction significantly influenced the gut microbiota in rats, while physical activity had only marginal effects (Trinh et al. 2021).

β-diversity is a common measure in microbiome research to investigate the similarity of microbiota between samples (Lagkouvardos et al. 2017). It confirmed the difference between food-restricted animals and normally fed controls supporting that food reduction seems to be the driving factor for gut microbiota alterations rather than running-wheel activity (Trinh et al. 2021). In our study, six genera were of particular interest as they showed major shifts in relative abundance after chronic starvation. The relative abundance of the genus *Prevotella* was decreased, while the relative abundances of the genera *Odoribacter*, *Lactobacillus*, *Akkermansia*, *Bifidobacterium,* and *Ruminococcus* were increased after starvation (Trinh et al. 2021). Heterogeneous results regarding changes in single genera between patients with AN and controls or food-restricted animals and controls have been observed in previous studies that could be explained by the multifactorial genesis of AN and methodological differences in the study design. However, high levels of relative abundance of the genus *Akkermansia* were observed several times in patients with AN and in animal studies of starvation (Derrien et al. 2017; Mack et al. 2016; Remely et al. 2015; Sonoyama et al. 2009; Trinh et al. 2021). *Akkermansia* is a mucin-utilizing bacterium that belongs to the phylum *Verrucomicrobia* (Derrien et al. 2017; Mack et al. 2016). On the one hand, degradation of mucins covering the gut wall during a state of starvation is a competitive benefit compared to other microbiota that are dependent on dietary nutrients. On the other hand, however, it might increase intestinal permeability by damaging the protective mucus layer. The latter can lead to increased passage of bacterial components and products across the

gut wall representing one possible pathway of the gut-brain axis (Mack et al. 2016; Seitz et al. 2019).

Regarding the gut-brain axis and altered brain morphology, we observed various associations between changes in the gut microbiota and volumetric and cellular brain parameters in food-restricted rats. Starved rats with high relative abundances of *Odoribacter* and *Bifidobacterium* showed lower levels of GFAP (glial fibrillary acidic protein) mRNA expression in white brain matter (corpus callosum) (Trinh et al. 2021), potentially contributing to the striking reduction in astrocytes described above. Furthermore, high relative abundances of *Lactobacillus* were associated with bigger brain volumes in the cerebral cortex and the corpus callosum (Trinh et al. 2021), potentially limiting the severe brain volume reduction found previously in patients with AN and in the ABA model by our group and others (Frintrop et al. 2017, 2019; Seitz et al. 2016). As described above, brain volume reductions in the ABA paradigm were linked to loss of GFAP$^+$ astrocytes (Frintrop et al. 2017, 2019). In order to prove a causal relationship between these observations, fecal microbiota transplantation transferring gut microbiota isolated from patients with AN in microbiota-free animals is needed. Additionally, supplementation with *Odoribacter* and *Bifidobacterium* is of interest to study their causal role in GFAP$^+$ astrocyte reduction. Probiotic substitution with *Lactobacillus* could represent an interesting option to study its effect on limiting brain volume loss, which would be easily transferrable to patients given successful animal experiments.

The Microbiome: Astrocytes

What are potential mechanisms that could mediate these associations of microbiota with the brain in AN? Specific research in AN is currently lacking; however, general mechanisms influencing cells in the brain include the vagal nerve, bacterial components or metabolites, immunological effects, and intestinal hormones or neurotransmitters that are able to cross the blood-brain barrier (Erny et al. 2017). From studies with germ-free animals that lack any bacterial colonization, it is clear that gut microbiota affects brain physiology. Germ-free mice, for example, show increased numbers of immature microglia with altered morphology including increased branching and longer processes compared to microglia in conventionally raised mice (Fung et al. 2017).

The activity of astrocytes seems to be influenced via microbial metabolites that activate the astrocytic aryl hydrocarbon receptor (AHR) (Fung et al. 2017; Rothhammer et al. 2016). Activation of this ligand-activated transcription factor decreases inflammation through the regulation of type 1 interferon signaling in astrocytes. Dietary tryptophan is metabolized by gut bacteria leading to the production of indole-3-aldehyde and indole-3-propionic acid that act as natural AHR agonist and thereby have a relevant effect on the inflammatory status of astrocytes and general neuroinflammation (Fung et al. 2017). As an example, *Lactobacillus reuteri*,

a commonly used probiotic supplementation, is known to produce indole-3-aldehyde from dietary tryptophan (Zelante et al. 2013) and could thus influence AHR.

Furthermore, inflammatory Ly6C^{hi} monocytes have been shown to link changes in gut microbiota with cell neurogenesis in the brain and related learning capabilities (Mohle et al. 2016). The treatment of mice with antibiotics leads to loss of hippocampal neurogenesis and memory consolidation at least partially mediated by Ly6C^{hi} monocytes. Probiotic treatment with specific microbial species, in contrast, was able to restore these deficiencies in neurogenesis and learning in mice (Mohle et al. 2016).

A study by Margineanu showed that genes implicated in the astrocyte-neuron lactate shuttle (ANLS) are modulated by gut bacteria (Margineanu et al. 2020). The ANLS hypothesis states that neurons are mainly oxidative and astrocytes are mainly glycolytic cells and implies intercellular lactate transport from astrocytes to neurons for further oxidation of lactate in neurons via the citric acid cycle (Pellerin et al. 1998). By investigating mRNA expression levels of ANLS-associated genes in the hippocampus of germ-free mice, germ-free mice colonized with gut microbiota, and conventionally raised mice, a regulatory role of gut microbiota in the cellular metabolism in the brain was suggested (Hoban and Stilling 2018; Margineanu et al. 2020; Matsumoto et al. 2013). Summing up, these observations propose that gut microbiota and especially microbial metabolites may affect inflammatory and metabolic activities in the brain and especially in astrocytes. In future research, gut microbiota-targeted interventions such as dietary supplementation, pre- and probiotic treatment, and fecal microbiota transplantation might be shown to help treat AN and other psychiatric disorders.

Conclusion and Outlook

We showed that astrocyte loss could underlie the striking brain volume reduction in AN with multiple functional implications potentially including reduced learning capacity, mood changes, and sleep alterations, possibly helping to explain difficulties in psychotherapy of patients in the acutely starved state. Underlying mechanisms of this astrocyte loss include reduced neogenesis in line with the catabolic state in semi-starvation and probably involve consequences of reduced gonadal steroid hormones as well as inflammatory responses. Altered gut microbiota interactions with the brain could contribute to these numeric and functional astrocyte alterations. These results help to understand the underlying pathophysiology of AN and potentially brain-based consequences in other diseases involving cachexia like oncologic diseases and chronic inflammatory bowel diseases or of malnourished patients in developing countries and can be the basis of more astrocyte-centered research lines.

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Part VI
Targeting Astrocytes in Therapeutic Management of Neuropsychiatric Disorders

Astroglial Serotonin Receptors as the Central Target of Classic Antidepressants

Alexei Verkhratsky, Vladimir Parpura, Caterina Scuderi, and Baoman Li

Introduction

Major depressive disorder (MDD) belongs to severe mood disorders. Global prevalence of MDD is about 4.7% with regional differences (Ferrari et al. 2013; Steel et al. 2014). The lifetime prevalence varies from 3.3% to 16% across countries (Gu et al. 2013; Otte et al. 2016). It has been estimated that MDD will be a leading cause of disability by 2030 (Mathers and Loncar 2006). MDD is associated with great individual and family suffering, disability, poor daily functioning, insomnia, and negative prognosis for comorbid medical conditions (Fröjd et al. 2008; Buysse et al. 2008; Lynch and Clarke 2006; Kupfer et al. 2012). MDD is also associated with an elevated risk of suicide, psychotic presentations (Penninx 2017; Kendler et al. 2009), and other psychiatric disorders (Cassano et al. 2004). Treating MDD usually involves pharmacological agents and/or psychotherapy. Treatment coverage of MDD has clear regional differences: the coverage of treatment of psychiatric

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disorders including MDD varies between 7.0% and 20.3% across countries (Bijl et al. 2003; Demyttenaere et al. 2004). In the United States, less than 30% of adults who are positively screened for depression received any treatment (Olfson et al. 2016). In China, the discordant treatment ranges from 4% to 60% of MDD patients who ever received psychosocial therapy or pharmacotherapy (Yu et al. 2015; Liu et al. 2017; Chin et al. 2015). Overall, variations in epidemiology, clinical presentation, and treatment of MDD are significantly influenced by sociocultural and economic factors (Kleinman 2004; Compton et al. 2006; Zhong et al. 2018).

In the 1950s, imipramine and iproniazid were used, for the first time, for the pharmacotherapy of MDD, thus opening the history of antidepressant treatment (López-Muñoz and Alamo 2009). Consequently, these two agents contributed to the formulation of the first mechanistic hypothesis of depressive disorders, the monoaminergic theory. In the 1960s, the catecholamine hypothesis was further advanced, with the role of noradrenergic imbalance suggested to be the key pathological factor in the occurrence of MDD (Schildkraut 1965). Serotonin was at the focus of these hypotheses, which resulted in the invention of fluoxetine, the first selective serotonin reuptake inhibitor (SSRI). In recent decades, pathophysiological research of depression allowed pharmacological treatments to target specific neurotransmitters as well as the specific brain regions and types of MDD (Kutzer et al. 2020). For example, ketamine and esketamine are proposed to treat resistant depression (Abdallah et al. 2015; Stenovec et al. 2020), while brexanolone, a natural steroid, is the first Food and Drug Administration (FDA)-approved therapeutic medication of postpartum depression (Meltzer-Brody et al. 2018).

Despite considerable advances in studying MDD pathophysiology in recent decades, and an abundance of pharmacological agents approved for MDD treatment, a substantial number of MDD patients remains resistant to available antidepressants. A real-life sequential treatment study demonstrates that nearly 30% of MDD patients fail to achieve remission, even after multiple treatment attempts (Rush et al. 2004, 2006). This may reflect the fact that existing theories cannot fully explain pathological mechanisms of MDD; similarly, pharmacological mechanisms of action of available antidepressants are in need of further research. Overreliance on the monoaminergic hypothesis may stipulate limited success of antidepressants (Ceskova 2016; Ceskova and Silhan 2018).

Growing evidence supports the key role of astrocytes in the pathophysiology and pharmacology of MDD. Astrocytes are homeostatic cells of the central nervous system (CNS). They control multiple aspects of brain physiology at all levels of organization from molecular to organ and systemic (Verkhratsky and Butt 2013; Verkhratsky and Parpura 2015; Verkhratsky and Nedergaard 2018). An individual protoplasmic astrocyte interacts with as many as 100,000 synapses in mice and possibly up to 2,000,000 synapses in humans (Bushong et al. 2002; Oberheim et al. 2009); these astrocytic perisynaptic structures, known as synaptic cradle (Verkhratsky and Nedergaard 2014), are fundamental for maintaining neurotransmission in the CNS. Pathological changes in astrocytes, classified into astrogliosis, astrodegeneration, or atrophy with loss of function, are salient features of all neurological disorders (Pekny et al. 2016; Verkhratsky et al. 2017) including

neurodevelopmental (Zeidán-Chuliá et al. 2014) and neuropsychiatric (Verkhratsky et al. 2014; Peng et al. 2015, 2016) disorders. Based on reports of decreased astroglial numbers in postmortem histopathological studies of MDD patients, the dysfunction of astrocytes was postulated to contribute to the pathophysiology of depression (Cotter et al. 2001; Rajkowska et al. 2007; Hercher et al. 2009; Verkhratsky et al. 2014).

Expression of multiple receptors and transporters makes astrocytes potential targets for specific therapy, and indeed, astrocytes respond to many antidepressants (Hertz et al. 2014; Saura et al. 1992; Zhang et al. 2010). Astrocytes possess serotonin receptor subtypes associated with the pharmacology and pathophysiology of depression (Hertz et al. 2010, 2015; Ding et al. 2013; Kirischuk et al. 1996). In this chapter, we focus on astrocytic serotonin receptors and discuss their relation to MDD.

Serotonin Receptors in the Treatments of MDD

A multitude of neurotransmitter receptors is expressed in astrocytes, including ionotropic and metabotropic glutamate receptors, purinoceptors, α/β-adrenoceptors, and serotonin receptors (Hertz et al. 2015), all associated with the intracellular excitability (Verkhratsky and Parpura 2010; Verkhratsky et al. 2020, 2021). Astrocytic serotonin receptors are of particular importance for MDD because of the widespread application of SSRIs in clinical practice. Stimulation of serotonin receptors in astrocytes activates cytosolic and nuclear signaling pathways, altering cellular functions as well as gene expression (Peng et al. 2015).

There are seven subtypes of serotonin receptors designated as 5-HT_{1A-1F}, 5-HT_{2A-2C}, 5-HT_3, 5-HT_4, 5-HT_{5A}, 5-HT_6, and 5-HT_7. Among these subtypes, 5-HT_{1A-1F}, 5-HT_{2A-2C}, 5-HT_6, and 5-HT_7 receptors were discovered in cerebral or spinal astrocytes in humans and rodents (Hirst et al. 1997, 1998; Meuser et al. 2002; Merzak et al. 1996; Li et al. 2012). These serotonin receptors can be involved in the pathophysiology of MDD through numerous cellular signaling pathways. All astrocytic serotonin receptors are G-coupled protein receptors being linked to phospholipase C and inositol-1,4,5-trisphosphate ($InsP_3$)-dependent Ca^{2+} signaling (Verkhratsky et al. 2012).

5-HT_1 Receptors

The 5-HT_{1A} and 5-HT_{1B} receptors attract particular attention because of their involvement in the pathophysiology of MDD; these receptors are also pharmacological targets in the clinical therapeutics of depression (Moret and Briley 2000; Murrough et al. 2011; Murrough and Neumeister 2011; Ruf and Bhagwagar 2009; Sari 2004; Savitz et al. 2009; Tiger et al. 2014). The 5-HT_{1A} and 5-HT_{1B} receptors display 43% amino acid sequence homology, and both are the $G_{i/o}$

protein-coupled receptors (Hoyer et al. 2002). These receptor subtypes have different cellular localizations, with 5-HT_{1A} receptors mainly expressed in somata and dendrites (Sotelo et al. 1990) and 5-HT_{1B} receptors being primarily localized in axon terminals (Boschert et al. 1994). Furthermore, 5-HT_{1A} receptor is one of the most abundant in cortical regions implicated in mood and emotion (Albert and François 2010; Albert and Lemonde 2004). The 5-HT_{1B} receptors are widely distributed throughout the brain regions, with particularly dense expression in the substantia nigra and globus pallidus (Bonaventure et al. 1997; Varnäs et al. 2011).

The 5-HT_{1A} receptors act as autoreceptors and heteroreceptors. The presynaptic 5-HT_{1A} receptors are mainly the autoreceptors localized in the cell bodies and dendrites of serotonergic neurones in dorsal raphe nuclei. These 5-HT_{1A} receptors modulate the release of serotonin and cell discharge rates. Stimulation of 5-HT_{1A} autoreceptors decreases the firing activity of central serotonergic neurones and synthesis and release of serotonin by a negative feedback mechanism while promoting the depressive-like behaviors and the resistance responses to antidepressants, thus inhibiting their activity and having opposite results (Richardson-Jones et al. 2010, 2011; Milak et al. 2018). The postsynaptic 5-HT_{1A} receptors are heteroreceptors, localized in glutamatergic and γ-aminobutyric acid (GABA)-ergic neurones; these receptors show substantial expression in the hippocampus, medial septum, prefrontal cortex, and midbrain ventral tegmental regions where they regulate the release of acetylcholine, glutamate, and dopamine (Comley et al. 2015; Borroto-Escuela et al. 2018; López-Gil et al. 2008; Jeltsch-David et al. 2010; Di Matteo et al. 2008). The 5-HT_{1A} heteroreceptors play key roles in desensitization of postsynaptic 5-HT_{1A} receptors, especially in prefrontal cortex regions (Taciak et al. 2018; Naumenko et al. 2014). Inhibition of 5-HT_{1A} presynaptic autoreceptors or stimulation of 5-HT_{1A} postsynaptic heteroreceptors may produce antidepressant effects, and hence 5-HT_{1A} receptor antagonists or agonists may act as antidepressants or antidepressants potentiators, respectively (Richardson-Jones et al. 2011; Philippe et al. 2018).

There are indeed novel antidepressants based on 5-HT_{1A} receptor agonism; these include YL-0919, brexpiprazole, vilazodone, and vortioxetine hydrobromide. Some of these 5-HT_{1A} receptor agonists also act as SSRIs and as agonists or antagonists of other serotonin subunits. For example, vortioxetine hydrobromide is the agonist of 5-HT_{1A} receptor and SSRI; it is a partial agonist of 5-HT_{1B} receptors and antagonist of 5-HT_3 and 5-HT_7 receptors (Wang et al. 2019). Compound MIN-117, an antagonist of 5-HT_{1A} autoreceptors, is considered for adjunctive therapy to improve acute antidepressant effects of SSRIs (Artigas et al. 2001; Sahli et al. 2016).

Similar to 5-HT_{1A} receptors, 5-HT_{1B} receptors are classified into autoreceptors and heteroreceptors. In postmortem tissue from the suicide MDD subjects, the level of 5-HT_{1B} receptors is decreased in the hippocampus; the mRNA of 5-HT_{1B} receptors is also lower in the frontal cortex. Conversely, mRNA of 5-HT_{1B} receptors is higher in the hypothalamus, compared with a healthy group (Anisman et al. 2008). Serotonin binding to the 5-HT_{1B} receptors in serotonergic neurones decreases the formation of cAMP and the downstream signaling responses, which results in the reduction of transmitter release (Barnes and Sharp 1999; Leenders and Sheng 2005;

Middlemiss and Hutson 1990). Furthermore, 5-HT_{1B} receptors could modulate serotonin transporters (SERT), and thus 5-HT_{1B} autoreceptors can regulate the serotonin release from serotonergic neurones (Hagan et al. 2012; Montañez et al. 2013). An agonist of 5-HT_{1B} receptor CP-93129 decreases 5-HT release in the hippocampus in rats (Hjorth and Tao 1991). In the hippocampus and cortex of wild-type mice, an agonist of 5-HT_{1B} receptor decreases the level of serotonin, while an antagonist of this receptor has the opposite effect on the serotonin level. Both effects are diminished in the transgenic mice with genetically deleted 5-HT_{1B} receptors (Rutz et al. 2006). In addition, 5-HT_{1B} receptors localized in non-serotonergic neurones can modulate the release of glutamate, GABA, acetylcholine, and dopamine (Ruf and Bhagwagar 2009).

Serotonin release is suppressed by 5-HT_{1B} receptor antagonists SB-616234-A (Dawson et al. 2006), AZD3783 (Zhang et al. 2011), and AR-A000002 (Hudzik et al. 2003), which makes them candidates for antidepressive therapeutics. Stimulation of 5-HT_1 receptors may neutralize the positive effects of SSRIs on serotonin levels to produce the therapeutic latency (Blier and de Montigny 1994; Nutt 2002). Therefore, the antagonists of 5-HT_{1B} receptors may act as rapid antidepressants. Available 5-HT_{1B} receptor antagonists are not sufficiently effective as antidepressants but can be used as potential adjuvants (Ruf and Bhagwagar 2009). As a result, the combination of SSRIs with 5-HT_{1B} receptor antagonists represents a new therapeutic scheme for MDD (Matzen et al. 2000).

5-HT_2 Receptors

The 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors are G_q protein-coupled receptors, which activate phospholipase C (PLC) or protein kinase C and trigger rapid $InsP_3$-dependent Ca^{2+} signaling or stimulate phospholipase A2 (PLA2) thus increasing arachidonic acid release (Masson et al. 2012; Li et al. 2008). The link between 5-HT_{2A} receptors and astrocytes emerged in 1999 when 5-HT_{2A} receptors were found to be significantly upregulated in reactive astrocytes (Wu et al. 1999). Trazodone, a triazolopyridine derivative, could play a neuroprotective role by inhibiting 5-$HT_{2A/2C}$ receptors in human reactive astrocytes, while fluoxetine also has a similar neuroprotective effects by blocking the same receptors (Daniele et al. 2015). Antagonists of 5-HT_{2A} receptors such as EMD281014, FG5893a, and M100907 suppress depressive-like behavior as reported by forced swim test, the classical rodent behavioral test for depressive phenotype (Patel et al. 2004; Albinsson et al. 1994; Marek et al. 2005). Antagonist of 5-HT_{2A} receptors promotes noradrenaline release under SSRI treatment (Dremencov et al. 2007), suggesting a feedback loop between 5-HT_{1A} receptors in glutamatergic neurones and 5-HT_{2A} receptors in GABAergic neurones. Such interaction may enhance the antidepressant activity of SSRIs and noradrenaline reuptake inhibitor (SNRIs) YM992, which is a potent 5-HT_{2A} antagonist (Szabo and Blier 2002). Some recent studies show that functional

disruption of the 5-HT_{2A} receptors may be related to postpartum depression disorder or psychotic disorders (Gao et al. 2018).

Even though 5-HT_{2A} receptors are widely researched with regard to the pharmacological mechanism of antidepressant action, most research focusses on neurones (Szabo and Blier 2001a, b). However, fluoxetine does not affect the mRNA expression of 5-HT_{2A} receptors in neurones or astrocytes, isolated and sorted from transgenic mice treated with chronic unpredictable mild stress (Li et al. 2012). In contrast, astrocytic 5-HT_{2B} receptors have shown significant changes.

Fluoxetine increases mRNA expression of 5-HT_{2B} receptors decreased by the treatment with chronic stress solely in astrocytes, and not in neurones (Dong et al. 2015; Li et al. 2012). Similarly, in the Parkinson's disease model, 5-HT_{2B} receptors are downregulated in astrocytes, but not in neurones; this downregulation develops in parallel with depressive-like behaviors (Diaz et al. 2016). The 5-HT_{2B} receptor is widely distributed in mammalian brains, including the frontal cortex, septal nuclei, dorsal hypothalamus, and medial amygdala (Duxon et al. 1997; Kursar et al. 1994; Li et al. 2012; Dong et al. 2015). In the primary cultured astrocytes or in the fluorescence-activated cell sorted astrocytes from *hgfap*::EGFP transgenic mice (expressing enhanced green fluorescence protein driven by a fragment of the human glial fibrillary acidic protein promoter), 5-HT_{2B} receptors are co-expressed with 5-HT_{2A} and 5-HT_{2C} receptors (Li et al. 2012; Hertz et al. 2010). However, astrocytic 5-HT_{2B} receptor has a much higher affinity for serotonin than the other two 5-HT_2 receptors subtypes (Li et al. 2010). Stimulation of 5-HT_{2B} receptors with 1 nM serotonin triggers phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2), while 5-HT_{2C} receptor-mediated ERK1/2 phosphorylation occurs at 100 nM, and 5-HT_{2A} receptors are activated by serotonin in concentrations above 10μM (Li et al. 2010). All SSRIs including fluoxetine act as agonists of astrocytic 5-HT_{2B} receptors suggesting the role of these receptors in antidepressive action (Zhang et al. 2010; Hertz et al. 2012; Li et al. 2009a, 2012, 2017).

Astrocytic 5-HT_{2B} receptors treated with various concentrations of fluoxetine trigger different signaling pathways to regulate gene expressions. Acute treatment with fluoxetine at concentrations lower than 1μM decreases mRNA expression of c-Fos through phosphoinositide 3 kinase(PI3K)-protein kinase B (also known as AKT) signaling pathway; at higher concentrations (more than 5μM), however, fluoxetine elevates this gene expression by mitogen-activated protein kinase (MAPK)-ERK signaling pathway (Fig. 1; Li et al. 2017). Stimulation of 5-HT_{2B} receptors by fluoxetine in astrocytes leads to the transactivation of epidermal growth factor receptors (EGFR); this in turn activates downstream MAPK/ERK or PI3K/AKT signaling cascades thus regulating expressions of genes possibly related to mood disorders. These genes include Ca^{2+}-dependent phospholipase A2 (cPLA2), subtype 2 of adenosine deaminases acting on RNA's (ADAR2), or subtype 2 of kainate receptors (GluK2) (Li et al. 2009b, 2011, 2012; Rao et al. 2006). Chronic treatment with fluoxetine also induces RNA editing of ADAR2, resulting in the loss of function of 5-HT_{2B} receptors, although expression of these receptors is increased (Peng et al. 2014). Rapid increase in $[Ca^{2+}]_i$ triggered by an agonist of 5-HT_{2B} receptors was suppressed by chronic treatment with fluoxetine (Li et al. 2011; Peng

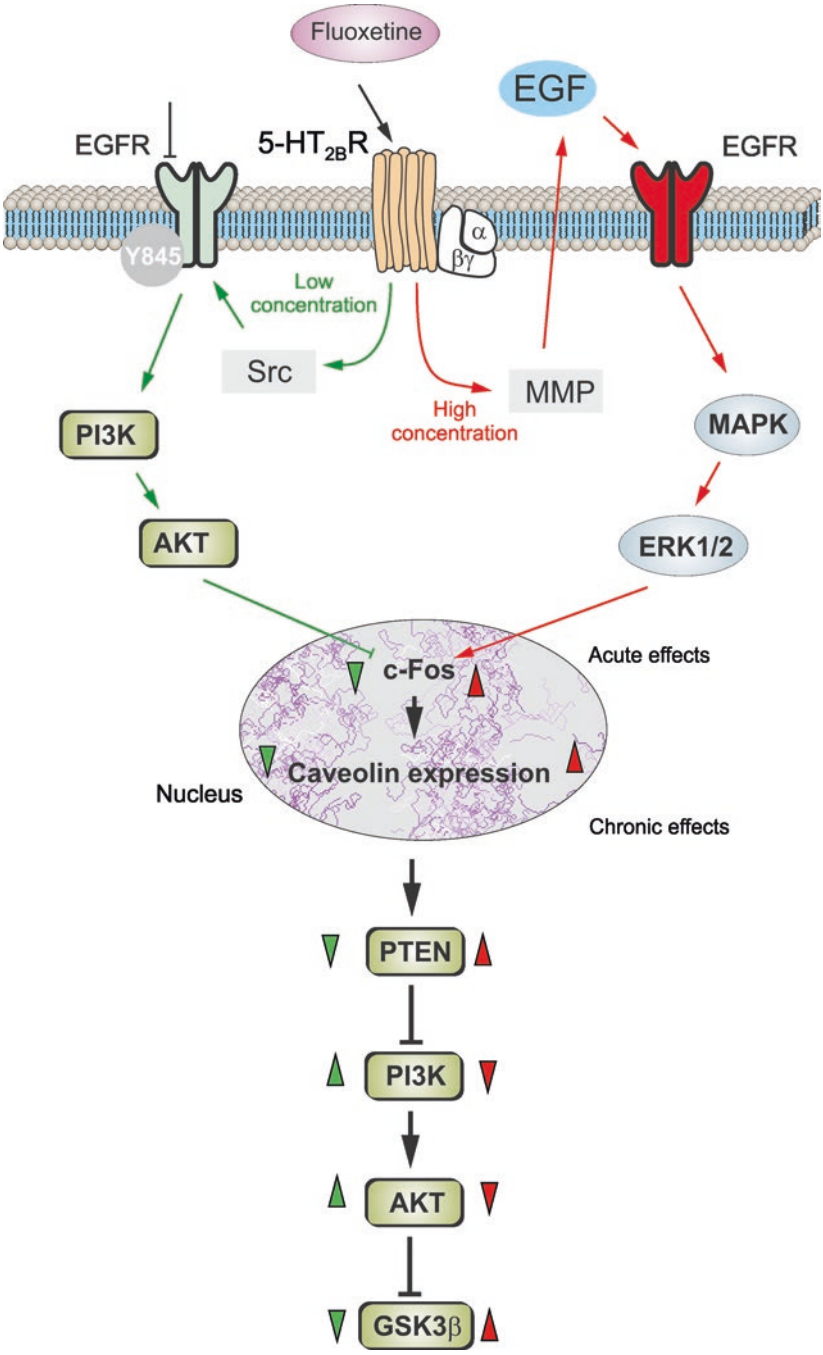

Fig. 1 Schematic illustration of biphasic concentration-dependent regulation of Cav-1 gene expression and GSK-3β activity by fluoxetine in astrocytes. Fluoxetine is an agonist to serotonin 2B receptors (5-HT_{2B}R). Acute treatment with fluoxetine at low concentrations (green arrows)

et al. 2014). Malfunction of 5-HT_{2B} receptors has been discovered in chronic stress animal models of depression and in animals with depressive-like behaviors associated with Parkinson's disease or hyperammonemia (Li et al. 2012; Zhang et al. 2015; Yue et al. 2019). This evidence indicates that 5-HT_{2B} receptors are a target for SSRIs, and it is indicative of the potential contribution of astrocytic 5-HT_{2B} receptors to the pathophysiology of MDD (Kennett et al. 1996, 1998). Agonist of 5-HT_{2B} receptors BW723C86 displays anxiolytic-like effects, whereas 5-$HT_{2C/2B}$ receptor antagonist SB200646A improves depressive-like behaviors (Kennett et al. 1995).

The 5-HT_{2C} receptors are upregulated by fluoxetine specifically in neurones sorted from *Thy1*::YFP transgenic mice, expressing yellow fluorescence protein driven by Thy1 promoter (Li et al. 2012). Antagonist of 5-HT_{2C} receptor S32006 demonstrates antidepressive effects and increases the level of dopamine and noradrenaline in the frontal cortex in rats (Dekeyne et al. 2008). An inverse agonist of 5-HT_{2C} receptor, S32212, also has antidepressant activity in behavioral tests (Dekeyne et al. 2012). Fluoxetine is reported to act as an antagonist of 5-HT_{2C} receptors (Ni and Miledi 1997), while chronic treatment with SSRIs may promote receptor desensitization (Yamauchi et al. 2004). Mianserin and several classical tricyclic antidepressants (TCAs), such as amitriptyline, imipramine, and clomipramine, all work as antagonists with moderate to high affinity at 5-HT_{2C} receptors (Jenck et al. 1993; Millan 2005). SNRIs desipramine and maprotiline as well as atypical antidepressants mirtazapine, trazodone, and nefazodone similarly act as 5-HT_{2C} antagonists (Ni and Miledi 1997).

Increased density of 5-HT_{2C} receptors was found in the frontal cortex of subjects who committed suicide (Pandey et al. 2006). This increase may reflect changes in mRNA alternative splicing and/or RNA editing (Martin et al. 2013), which has been proposed as a risk factor for suicidal attempts (Dracheva et al. 2008). Clinical studies similarly indicated increases in mRNA editing of 5-HT_{2C} receptors in the frontal cortex of depressed suicide individuals (Niswender et al. 2001; Gurevich et al. 2002; Iwamoto and Kato 2003; Schmauss 2003). A recent study demonstrated that astrocytic 5-HT_{2C} receptors are involved in the depressive- and anxious-like behaviors induced by alcohol addiction. Fluoxetine at low concentration (1μM) can alleviate these anxiety-like behaviors and motor activity induced by alcohol by

Fig. 1 (continued) stimulates Src which phosphorylates epidermal growth factor (EGF) receptors (EGFR) at Y845 residue and in turn activates phosphoinositide 3 kinase (PI3K)-AKT signaling pathway. The AKT phosphorylation by fluoxetine at low concentrations inhibits c-Fos gene expression and subsequently decreases caveolin-1 (Cav-1) gene expression (chronic effects) that in turn decreases membrane content of PTEN (phosphatase and tensin homolog), induces phosphorylation and stimulation of PI3K, and elevates glycogen synthase kinase 3 (GSK-3β) phosphorylation thus suppressing its activity. At higher concentrations, fluoxetine (red arrows) stimulates metalloproteinase (MMP) and induces shedding of growth factor which stimulates EGFR and activates mitogen-activated protein kinase (MAPK) extracellular signal-regulated kinases 1/2 (ERK1/2) signal pathway. The ERK1/2 phosphorylation by fluoxetine at high concentrations stimulates cFos gene expression and subsequently increases Cav-1 gene expression (chronic effects), which acts on PTEN/PI3K/AKT/GSK-3β in an inverse fashion. (From Li et al. 2017)

suppressing the expression of ADAR2 and mRNA editing of 5-HT_{2C} receptors (Li et al. 2020).

The study in chronic social defeat animal model of depression reported increased sensitivity of 5-HT_{2C} receptors that can be reversed by chronic antidepressants (Berton et al. 2006; Rygula et al. 2005, 2006). Pretreatment with 5-HT_{2C} receptor agonist m-chlorophenylpiperazine increases behavioral presentations of defeat in hamsters (Harvey et al. 2012). In rats, however, chronic stress increases depressive-like behavior, this effect being arguably mediated through 5-HT_{2C} receptors (Kimura et al. 2008; Moreau et al. 1993). Suppression of dopamine release mediated by 5-HT_{2C} receptors has been observed in rat models of depression (Dremencov et al. 2005; Oba et al. 2013). Antagonists of 5-HT_{2C} receptors can alleviate stress-induced depressive-like behaviors in mice, while their antidepressive effects may relate to dopaminergic neurones in the ventral tegmental area (Opal et al. 2013). Chronic treatment with 5-HT_{2C} receptor agonist RO60-0175 alleviates anhedonia in stressed mice by desensitization of the receptor (Moreau et al. 1993). Depressive-like behaviors in the learned helplessness model can be improved by selective antagonists of 5-HT_{2C} receptors (Strong et al. 2009). Likewise, clomipramine, a potential antagonist of 5-HT_{2C} receptors, decreases elevated mRNA expression of 5-HT_{2C} receptors in chronic stress treated rats (Pitychoutis et al. 2012).

All these observations suggest that the dysfunctions of 5-HT_2 receptors may be a consequence of stress and can be linked to anxiety, depression, and suicide. Antidepressive effects of agonists and antagonists of 5-HT_2 receptors remain controversial and poorly understood, thus warranting more research.

Other Serotonin Receptors

The 5-HT_3 is the only ionotropic member of the serotonin receptors family. This 5HT-gated channel is assembled from five subunits, $5HT_{3A}$, $5HT_{3B}$, $5HT_{3D}$, $5HT_{3E}$, and $5HT_{3F}$, expression of which was confirmed in humans (Niesler et al. 2007). In rodents, however, only $5HT_{3A}$ and $5HT_{3B}$ subunits have been identified (Karnovsky et al. 2003). Ondansetron and zacopride, antagonists of $5HT_3$ receptors, have been used in clinical therapeutics of depression, and both reversed the depressive-like behaviors in the rat learned helplessness model (Martin et al. 1992; Thiebot and Martin 1991). Antagonists of $5HT_3$ receptors potentiate the pharmacological efficiency of clinical antidepressants (Nakagawa et al. 1998; Redrobe and Bourin 1997). Vortioxetine is a multimodal drug which binds to 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, and 5-HT_7 receptors and to SERT; it also acts as a potent antagonist of $5HT_3$ receptors. Vortioxetine demonstrated antidepressive effects in rodent models of depression (Guilloux et al. 2013; Mork et al. 2012; Wallace et al. 2014). Furthermore, preclinical data also show that vortioxetine as an antagonist of $5HT_3$ receptors produced antidepressant response faster than classical antidepressants (Bétry et al. 2013). In addition, vortioxetine demonstrates antidepressive performance in patients

resistant to SSRIs or SNRIs (Alvarez et al. 2014). $5HT_3$ receptor antagonists may be promising therapeutic agents, although certain unresolved issues remain, including those of heterogeneity of the species used and of the inconsistent data on effective doses as antidepressants (Adrien et al. 1992; Costall et al. 1987; Johnson et al. 2002, 2006; Martin et al. 1992; Ramamoorthy et al. 2008).

5-HT_4 receptors are widely distributed in limbic regions, such as the amygdala and hippocampus (Hannon and Hoyer 2008; Tanaka et al. 2012). Being G_s-coupled, 5-HT_4 receptors increase intracellular cAMP by stimulating adenylyl cyclase (Dumuis et al. 1988; Fagni et al. 1992). Decrease in 5-HT_4 receptors was observed in the striatum of depressed patients and in mice models (Amigó et al. 2016; Madsen et al. 2014). In postmortem studies of depressed suicide victims, various binding forms of 5-HT_4 receptors and the different levels of cAMP in distinct brain areas have been reported (Rosel et al. 2004). A selective partial agonist of 5-HT_4 receptors, RS67333, has a rapid antidepressant effect in chronic depression models of rodents (Lucas et al. 2007).

In MDD context, studies of 5-HT_5, 5-HT_6, and 5-HT_7 receptors are scarce. Administration of N-methyl-D-aspartate receptor antagonist ketamine, at a dose that leads to drug abuse, can trigger schizophrenic-like symptoms in animals (de la Salle et al. 2016). In these ketamine pretreated mice, an agonist of 5-HT_6 receptors E-6837 as well as an antagonist of these receptors SB-271046 can both produce depressive-like behaviors (Suárez-Santiago et al. 2017). Antagonists of 5-HT_7 receptors have faster antidepressant effects when compared to fluoxetine in the rat model of depression (Mnie-Filali et al. 2011).

To summarize, there are many uncertainties and controversies concerning MDD-related pharmacology of serotonin receptors. In general, agonists of 5-HT_{1A}, 5-HT_{2B}, and 5-HT_4 receptors and antagonists of 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_6, and 5-HT_7 act as antidepressants. None of these drugs, however, can substantially affect clinical manifestations of depression.

Astrocytes as a Target for Classic Antidepressants

Classic antidepressants are SSRIs, SNRIs, TCAs, inhibitors of monoamine oxidase (MAO), and lithium. Major theories of MDD pathophysiology focus on neurones, with particular emphasis on monoamines (Marathe et al. 2018), aberrant signaling of brain-derived neurotrophic factor (BDNF), leptin dysregulation (Milaneschi et al. 2017), *myo*-inositol abnormalities (Yu and Greenberg 2016), and glutamate homeostasis failure (Shirayama et al. 2017). Here, we discuss the MDD from the astrocytic angle and portray astrocytes as targets for therapy.

SSRIs

SSRIs, which include fluoxetine, fluvoxamine, sertraline, paroxetine, and citalopram, are the most popular antidepressants and anxiolytics. An increase in extracellular serotonin availability following SERT inhibition has been regarded as the main and the only pharmacological mechanism of SSRIs, despite the well-known delay in clinical effect contrasting to the immediate inhibition of SERT. Recently, the contribution of astrocytes to MDD has gained increased attention. Postmortem histological analysis of the frontal cortex reported a reduced number of glia in patients suffering from MDD (Cotter et al. 2001, 2002). Decreased density of neuroglia and decrease in glia-to-neurone ratio have also been observed in the amygdala (Bowley et al. 2002; Hamidi et al. 2004). Experimental ablation of astrocytes (but not neurones) in the frontal cortex is sufficient to initiate depressive-like behavior in rats (Banasr and Duman 2008). Similarly, loss of astrocyte-derived ATP induces depressive phenotypes in rodents (Cao et al. 2013). Fluoxetine reverses the loss of hippocampal astrocytes in an animal model of depression (Czéh et al. 2006), while increasing the release of ATP from astrocytes by regulating vesicular nucleotide transporter (Kinoshita et al. 2018).

Fluoxetine acts as an agonist of astrocytic 5-HT_{2B} receptors. However, acute and chronic treatments of astrocytes with fluoxetine produce different outcomes. Acute treatment with 10μM fluoxetine triggers Ca^{2+} signals, transactivates the EGFR, and phosphorylates downstream ERK1/2 signaling cascade; ERK1/2 enters nuclei and regulates the mRNA and protein expression of *c-Fos* and *FosB*, consequently modulating the expression of several key proteins (Li et al. 2008). For instance, fluoxetine, by stimulating 5-HT_{2B} receptors, increases protein expression of cPLA2, GluK2, ADAR2, transient receptor potential canonical 1 channels, L-type $Ca_v1.2$ Ca^{2+} channels, caveolin-1, and BDNF (Li et al. 2009a, 2011, 2017, 2019; Hertz et al. 2015; Peng et al. 2018). Increased expression of ADAR2 in astrocytes following chronic treatment with fluoxetine catalyzes RNA editing, promoting loss of function of 5-HT_{2B} receptors and GluK2, which affects Ca^{2+} signaling and phosphorylation of ERK1/2 (Li et al. 2011; Hertz et al. 2012). Decreased expression of astrocytic 5-HT_{2B} receptors was also observed in chronic stress models and Parkinson's disease (Dong et al. 2015; Zhang et al. 2015). Fluoxetine can selectively upregulate the expression of 5-HT_{2B} receptors in astrocytes (Li et al. 2012). However, PI3K/AKT and MAPK/ERK signaling pathways induced by low and high concentrations of fluoxetine result in the opposite regulation of caveolin-1 and glycogen synthase kinase-3β (GSK-3β) (Fig. 1) (Li et al. 2017). Some effects of fluoxetine mediated by 5-HT_{2B} receptors may contribute to both therapeutic and adverse effects of this drug; hence, selective stimulation or inhibition of various signaling pathways triggered by fluoxetine may promote the efficacy or lessen the side effects of antidepressants.

Depressive disorders are associated with many neurological conditions including sleep disturbances, Alzheimer's, and Parkinson's diseases (Xia et al. 2018; Orgeta et al. 2017; Huang et al. 2019). Aging of astrocytes (Verkhratsky et al. 2020, 2021)

may contribute to age-dependent diseases as well as to depressive phenotypes. Sleep disturbance in particular is linked to both depression and neurodegeneration. Insomnia and depression can easily combine into a vicious cycle, as decreased sleep time increases the risk for MDD, which further exacerbates sleep disorders (Roberts and Duong 2014). The glymphatic system (Iliff et al. 2012) is responsible for the clearance of brain metabolite waste via paravascular pathways (Xie et al. 2013). Astrocytic endfeet forming *glia limitans vascularis* and endfeet-polarized expression of aquaporin 4 (AQP4) support the glymphatic system. In aging, astroglial atrophy decreases glymphatic clearance facilitating extracellular accumulation of disease-related proteins, such as β-amyloid (Kress et al. 2014). Increased accumulation of β-amyloid has been reported by positron emission tomography in the right hippocampus and thalamus of human subjects having their moods affected by sleep deprivation (Shokri-Kojori et al. 2018). In animals, chronic stress increases β-amyloid$_{42}$ in the frontal cortex and hippocampus. Fluoxetine upregulates the expression of AQP4 and promotes clearance of β-amyloid$_{42}$ by improving glymphatic clearance; this also rescues depressive-like behaviors (Xia et al. 2017). Toxic load with iron also impairs the glymphatic system, thus exacerbating depressive-like phenotypes and increasing neuronal apoptosis (Fig. 2; Liang et al. 2020).

Growing evidence indicates a strong link between sleep deprivation and activation of nucleotide-binding domain and leucine-rich repeat protein-3 (NLRP3) inflammasome; this activation is mediated by astrocytic P2X$_7$ receptors in astrocytes, and it facilitates neuronal apoptosis (Xia et al. 2018; Zielinski et al. 2017). Chronic sleep deprivation selectively downregulates expression of astrocytic 5-HT$_{2B}$ receptors, the effect of which is similarly mediated by P2X$_7$ receptors (Fig. 3; Xia et al. 2020). These changes result in depressive-like behaviors associated with the gradual elevation of extracellular ATP (Xia et al. 2020). Fluoxetine increases the phosphorylation of signal transducer and activator of transcription 3, thus suppressing astrocytic NLRP3 activation and neuronal apoptosis (Xia et al. 2018; Zielinski et al. 2017). Inhibition of astrocytic NLRP3 inflammasome by fluoxetine is also mediated by 5-HT$_{2B}$ receptors (Li et al. 2019). In addition, fluoxetine, again acting through 5-HT$_{2B}$ receptors, recovers BDNF levels suppressed by sleep deprivation (Li et al. 2019). Pre-treatment with the 16 kDa hormone leptin increases expression of astrocytic 5-HT$_{2B}$ receptors, thus enhancing positive effects of fluoxetine on BDNF and depressive-like behaviors (Li et al. 2019). Of note, long-term, chronic stress may induce sleep disorders and depression associated with decreased levels of BDNF (Schmitt et al. 2016).

Pathological features and pathogenesis of sleep disturbances, depressive disorders, and neurodegenerative pathology, such as Alzheimer's disease, usually overlap, and all these may be linked to astrocytes. Morphological and functional abnormalities of astrocytes can impair BDNF signaling and the glymphatic system, with failed glymphatic clearance being a key contributor to diseases of cognition (Nedergaard and Goldman 2020), which could further worsen the deposition of brain waste and impair neuronal functions. Fluoxetine and other SSRIs may provide neuroprotection by arresting astrogliopathology through direct stimulation of 5-HT$_{2B}$ receptors.

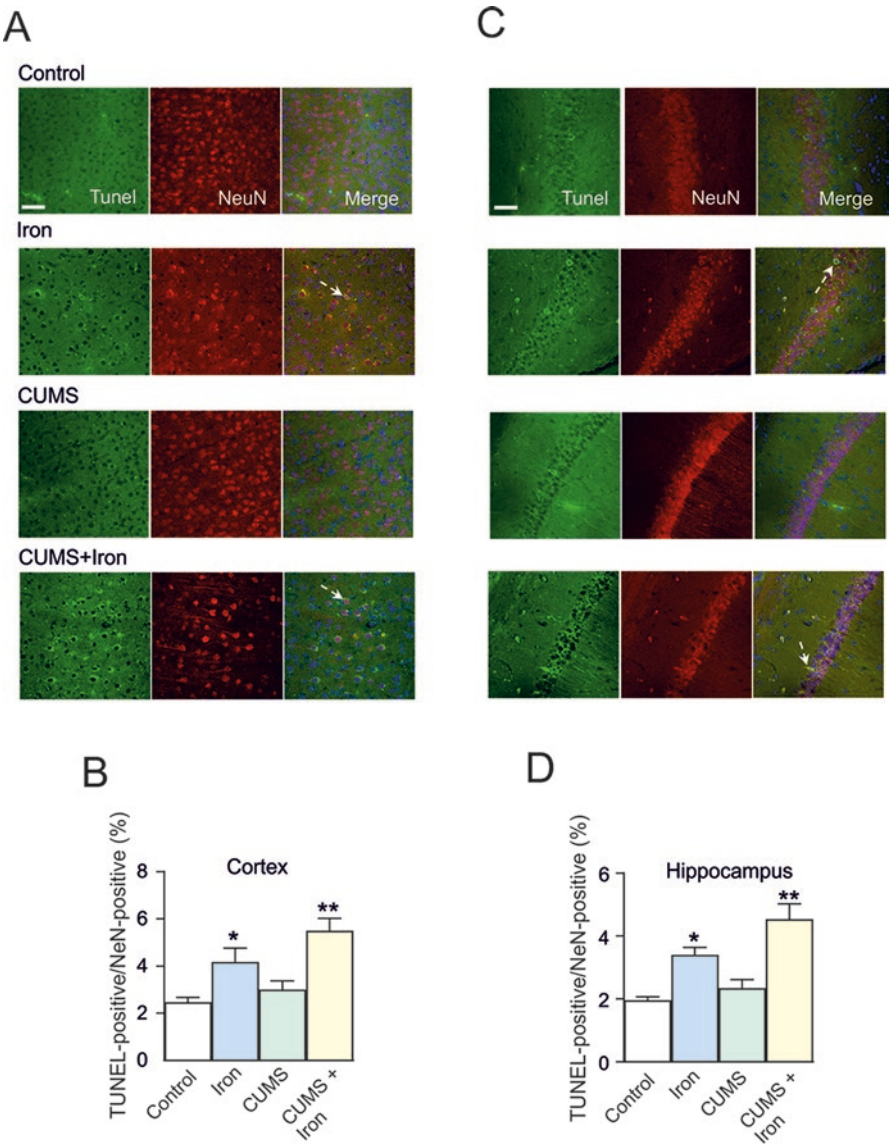

Fig. 2 Treatment with chronic stress enhances neuronal apoptosis triggered by overload with iron. Mice were pretreated without or with chronic unpredictable mild stress (CUMS) for 6 weeks; in week 6, animals were randomly separated to be injected with dextran (CUMS group) or iron dextran (CUMS+Iron group) for 6 days. Apoptosis was detected by TUNEL assay in the cortex (**a**) and hippocampus (**c**), where neuronal nuclei were stained with NeuN (red), while all the cell nuclei were labeled with DAPI (blue in merge). Percentage of cell death was determined by the ratio of TUNEL+ and NeuN+ cells, with the cortical and hippocampal regions analyzed in (**b**, **d**), respectively. Data are presented as mean ± SEM, $n = 6$. *$p < 0.05$, statistically significant difference compared with control, untreated group; **$p < 0.05$, statistically significant difference compared with any other group. (From Liang et al. 2020)

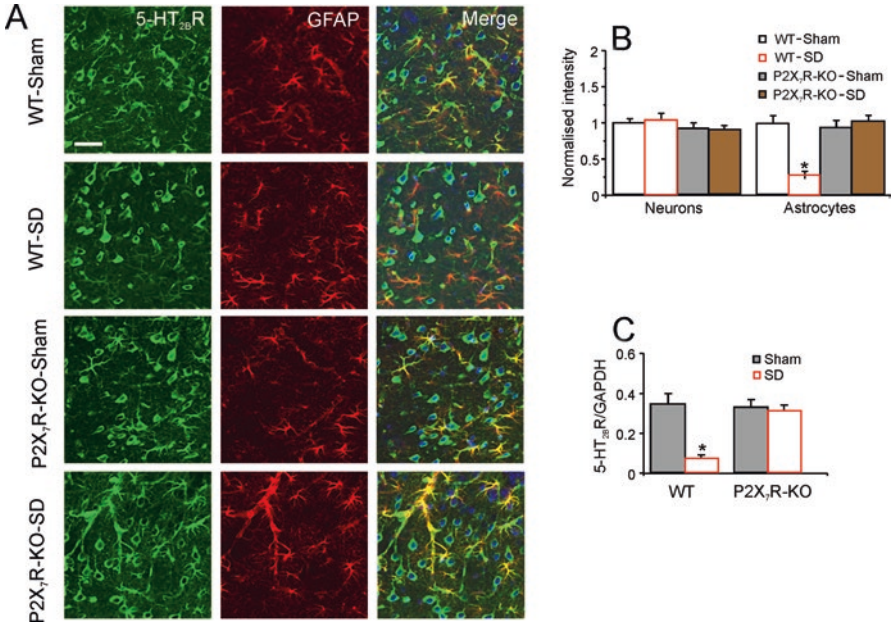

Fig. 3 $P2X_7$ receptors mediate the selective decrease of 5-HT_{2B} receptors in astrocytes treated with chronic sleep deprivation. (**a**) Immunolabelled 5-HT_{2B} receptors (green) were co-stained with glial fibrillary acidic protein (GFAP, red) and NeuN (blue) in the mice frontal cortex treated with sham (Control) or exposed to sleep deprivation for 3 weeks of wild-type (WT) and $P2X_7$ receptor knockout ($P2X_7$R-KO) mice. Scale bar, 20μm. (**b**) 5-HT_{2B} receptors immunolabeling intensity of neurones and astrocytes, respectively, relative to the cell-free parenchyma in the cortex, normalized to the intensity of a matching sham group. (**c**) RT-PCR analysis of 5-HT_{2B} receptors mRNA expression in WT or $P2X_7$R-KO mice treated with sleep deprivation for 3 weeks, expressed as the relative expression ratio of 5-HT_{2B} receptor/GAPDH, the latter used as loading control. Data represent mean ± SEM. *Indicates statistically significant ($p < 0.05$) difference from matching sham groups, $n = 6$. (From Xia et al. 2020)

SNRIs

Serotonin/noradrenaline reuptake inhibitors exert their effects through increasing availability of serotonin and noradrenaline in the nervous tissue, and they are commonly used to treat patients with refractory depression (Wang et al. 2014). Venlafaxine is one of the most commonly prescribed SNRI with a broad range of antidepressant effects. Accumulating evidence shows that venlafaxine may target astrocytes by affecting the metabolism of lysine, tyrosine, glutamate, methionine, ethanolamine, fructose-6-phosphate, and phosphorylethanolamine (Sun et al. 2017). Duloxetine, another SNRI widely used in the treatment of MDD (Nemeroff et al. 2002), was reported to suppress ischemia-induced astrocytic reactivity and oxidative stress (Lee et al. 2016).

TCAs and MAOIs

Astrocytic-derived neurotrophic growth factors receive attention because of their links to the mechanism of action of antidepressants (Tsybko et al. 2017). In primary cultured astrocytes, amitriptyline increases expression of BDNF, vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2), and glial cell line-derived neurotrophic factor (GDNF) (Kajitani et al. 2012). Furthermore, clomipramine (TCA), fluvoxamine (SSRI), and duloxetine (SNRI) all elevate the expression of FGF2 and BDNF in astrocytes (Hisaoka-Nakashima et al. 2016; Kajitani et al. 2012). Fluoxetine and paroxetine both enhance the mRNA expression of VEGF in primary astrocytes (Allaman et al. 2011).

Mirtazapine, a tetracyclic piperazinoazepine antidepressant, has a distinct pharmacological mechanism associated with inhibition of α_2-adrenoceptors and 5-HT_2 and 5-HT_3 receptors (Benjamin and Doraiswamy 2011; Croom et al. 2009). Unlike amitriptyline and other antidepressants, mirtazapine does not affect noradrenaline or serotonin reuptake (Al-Majed et al. 2018). Moreover, mirtazapine has a faster onset time as compared with SNRIs in the treatment of acute-phase MDD (Nagao et al. 2013; Watanabe et al. 2011). In primary culture of astrocytes, mirtazapine increases the expression of GDNF and BDNF by stimulating phosphorylation of $ERK^{1/2}$ (Hisaoka-Nakashima et al. 2016).

Astrocytes in Treatments of Bipolar Disorders

Therapeutic strategy for bipolar disorders (BD) is distinct from treating MDD, due to reflecting different pathophysiology. Lithium ion (Li^+) in various salts, valproic acid (VPA), and carbamazepine (CBZ) are three classical anti-bipolar drugs. Lithium salt was first to be used for treating mania and depressive episodes of bipolar depression; importantly, lithium may also prevent relapses (Brown and Tracy 2013). Both CBZ and VPA are used for treating manic episodes and epileptic seizures (Nevitt et al. 2019; Xu et al. 2019; Post et al. 2007). These three classical anti-BD drugs have nothing in common in their chemical structures, and only a few metabolic parameters in the brain are affected by them in a similar manner (Li et al. 2007). Revealing shared effects of these drugs is important because common mechanisms of action may provide information about the pathophysiology of BP and facilitate drug development.

Astroglial cell numbers in the cortex from BD patients are reduced (Ongür et al. 1998, 2008; Rajkowska 2000). This coincides with exaggerated activity of the glutamatergic system, as demonstrated by MRI, in the brains of BD patients (Ongür et al. 2008; Michael et al. 2003; Chen et al. 2010; Eastwood and Harrison 2010), which could be due to suppressed capacity of astrocytes to maintain glutamate homeostasis. In astrocytes, riluzole can increase the expression and activity of plasmalemmal glutamate transporters in order to increase the glutamate clearance from the extracellular space (Carbone et al. 2012). Riluzole can also improve the glutamine-glutamate cycle and the glutamatergic transmission in brains of BD patients (Brennan et al. 2010) and even alleviate related disease symptoms (Zarate

and Manji 2008), which is also indicative of potential astrocytic glutamatergic dysfunction.

We outline some common targets of these three classical anti-BD drugs on astrocytes. Firstly, the decreased expression of GluK2 was reported in the entorhinal cortex and the hippocampus of BD patients, most of whom had received drug therapy (Beneyto et al. 2007; Benes et al. 2001). In primary cultures of astrocytes treated with Li^+, VPA, or CBZ at clinically relevant doses the mRNA expression of GluK2 receptors decreased, whereas the expression of other subunits of GluK receptors remained unchanged (Li et al. 2009b). In vivo, after 2 weeks of intraperitoneal injection, CBZ reduced the gene expression of GluK2 which is encoded by *GRIK2* (Li et al. 2009b); of note, this gene in a genetic linkage region (6q21) is associated with BD (Schulze et al. 2004). In other studies, CBZ, VPA, or Li^+ suppresses GluK2-mediated phosphorylation of ERK1/2 in primary cultured astrocytes, while anticonvulsant topiramate is ineffective (Li et al. 2009b). Release of glutamate from astrocytes induced by ATP is inhibited by all three anti-BD drugs; this may suppress hyperactivity of the glutamatergic transmission in brains of patients with BD (Liu et al. 2015).

In addition to classical targets, Li^+ can play a key role in the metabolism of inositol. The intracellular myoinositol needs continuous re-supply from the diet (Spector and Lorenzo 1975) and de novo synthesis, which occurs in the vasculature (Wong et al. 1987). In primary culture of mouse astrocytes, chronic treatment with Li^+ at 1 mM inhibits the uptake of inositol, although this effect is absent during acute Li^+ treatment (Wolfson et al. 1998). Changes in myoinositol levels may have opposite effects depending on its concentration. For example, myoinositol at low concentration promotes the uptake of the extracellular inositol, whereas at high concentrations the uptake is inhibited. This may be related to the existence of two inositol transporters in astrocytes, the high-affinity Na^+-dependent myoinositol transporter (SMIT/SLC5A3), which accounts for most of the uptake at low (25μM) inositol concentration, and the lower-affinity H^+-dependent myoinositol transporter (HMIT/SLC2A13), which dominates the uptake at higher (50μM) inositol concentrations (Wolfson et al. 2000). Because the elevated intracellular pH (pH_i) stimulates SMIT but inhibits HMIT, the effects of anti-BD drugs on the inhibition of inositol may be caused by the intracellular alkalinization. This was further confirmed by studying the uptake of [^{3}H]myoinositol in astrocytes at various myoinositol doses or at various pH_i and corroborated by analysis of different myoinositol transporter operation (Fu et al. 2012). Chronic treatment by any of the three anti-BD drugs increases astrocytic pH_i (Song et al. 2008, 2013). The Na^+–H^+ exchanger (NHE) exchanger (NHE) is one of the acid-controlling transporters, widely distributed in almost all cell types, including neurones and astrocytes (McAlear and Bevensee 2006). The NHE/SLC9 family has seven subtypes, NHE1-NHE7. The NHE1/SLC9A1 is expressed in cultured astrocytes from the rat hippocampus (Pizzonia et al. 1996) and from the mouse cerebral cortex (Song et al. 2008). Chronic treatment with Li^+ at 1 mM alkalinize pH_i by about 0.10, but 0.5 mM is ineffective (Song et al. 2008).

The anti-bipolar effects of lithium are often attributed to the classical hypothesis of the depletion of myoinositol induced by Li^+ (Berridge et al. 1989). According to this hypothesis, Li^+ causes the non-competitive inhibition of inositol-phosphate

hydrolysis; $InsP_3$ is produced by PLC and degraded to myoinositol by inositol phosphatases, whereas diacylglycerol is converted to phosphatidate and condensed with cytidine triphosphate to form cytidine mono-phosphoryl-phosphatidate, which together with myoinositol regenerates phosphatidylinositol 4,5-bisphosphate (PIP_2) (Hallcher and Sherman 1980; Inhorn and Majerus 1987). Because Li^+ inhibits the formation of inositol from $InsP_3$, it decreases the regeneration of PIP_2 and blocks PLC pathway. The $[Ca^{2+}]_i$ response to noradrenaline in cultured astrocytes is suppressed by chronic treatments with Li^+ (Chen and Hertz 1996).

As astrocytes are the direct targets of Li^+, identification of the unique astroglial transcriptional networks is of importance. Recently, it was found that Li^+ can induce a specific astrocytic phenotype (Rivera and Butt 2019). By pharmacogenomic analyses, the roles of the extracellular matrix (ECM) regulatory enzyme lysyl oxidase (LOX) and peroxisome proliferator-activated receptor γ (PPAR-γ) were shown to modulate astrocyte morphogenesis. According to genomic analyses, LOX is the most highly regulated Li^+-responsive astroglial gene. Irreversible LOX inhibitor mimics effects of Li^+ suggesting that LOX is a major regulator of astrocyte morphology and proliferation. Treatment with Li^+ also actives PPAR-γ (Liu et al. 2011), while PPAR-γ has been reported to inhibit LOX (Segond et al. 2013). These effects may involve GSK3β-Wnt signaling, which is implicated in neuropsychiatric disorders and interacts with ECM remodeling. In addition, PPAR-γ agonists decrease TGF-β1 signaling leading to decreased fibrosis (Vallee et al. 2017), providing a further link with LOX and the actions of Li^+.

Neuroprotective effects of anti-bipolar drugs have been discovered in other neuronal diseases. Pretreatment with VPA increases expression of plasmalemmal glutamate transporter 1 (GLT-1) in astrocytes and promotes the recovery of locomotor activities in a rodent model (Johnson Jr et al. 2018). Lithium can mediate neuroprotection by inhibition of GSK3β after spinal cord injury (Li et al. 2018). Chronic treatment with Li^+ activates α1 subunit of neuronal Na^+-K^+-ATPase (Li et al. 2018). In contrast, chronic treatment with CBZ increases astrocyte specific α2 subunit containing Na^+/K^+ ATPase (Li et al. 2013).

Conclusion

In this chapter, we introduced the contribution of astrocytic serotonin receptors to the pathophysiology of MDD and to pharmacological mechanisms of classic antidepressants. Direct stimulation of astroglial $5\text{-}HT_{2B}$ receptors may be the common target of SSRIs. Activation of astrocytic serotonin receptors associates with several signaling pathways and regulates expression of numerous genes that are related to depressive-like behaviors. Recent discoveries overviewed in this chapter highlight the key roles of astrocytes in the pathogenesis and treatment of mood disorders.

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Ketamine Action on Astrocytes Provides New Insights into Rapid Antidepressant Mechanisms

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Astrocytes and Mood Disorders

Astrocytes are morphologically and functionally heterogeneous glial cells that principally provide homeostasis and defence of the central nervous system (CNS), the latter being associated with the evolutionary conserved program of reactive astrogliosis (Verkhratsky and Nedergaard 2018; Verkhratsky et al. 2017). During development, they (in the form of radial glia) guide migrating neurones towards neocortical destinations and instruct neurones to form synapses (Ullian et al. 2001). Throughout life, they promote survival of neurones (Seri et al. 2001) and signal back to them by the regulated release of gliosignalling molecules (Verkhratsky et al. 2016; Zorec et al. 2016) and factors that regulate synaptic connectivity and strength

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involved in learning and memory formation (Clarke and Barres 2013; Zorec et al. 2015). Being key providers of metabolites and growth factors, and acting as stabilizers of neuronal environment, impairment of astrocytes in pathology could destabilise operation of neural circuits in brain areas implicated in mood regulation. Unsurprisingly, numerous studies already highlighted the association between psychiatric disorders such as schizophrenia, bipolar disorder or major depressive disorder (MDD) and astrocytes (Dietz et al. 2020; Peng et al. 2016; Rajkowska and Stockmeier 2013; Verkhratsky and Nedergaard 2014). The abnormalities in the amount of glutamate at synapses controlled by astrocytes have also been linked to depression, anxiety and schizophrenia (Holden 2003). Besides glutamate, astrocytes recycle serotonin, dopamine and other monoamines implicated in psychiatric disorders.

Unlike in many other neurological conditions including neurotrauma or neurodegenerative disorders, astroglial atrophy and degeneration without signs of reactivity are characteristic in psychiatric disorders and MDD in particular (Rajkowska and Stockmeier 2013; Verkhratsky et al. 2014). In postmortem samples from depressed individuals, packing density or number of Nissl-stained populations of astrocytes is reduced (Bowley et al. 2002; Cotter et al. 2001, 2002; Gittins and Harrison 2011; Ongur et al. 1998; Rajkowska et al. 1999). These changes were observed in various brain regions including orbitofrontal cortex (Rajkowska et al. 1999), dorsolateral prefrontal cortex (Cotter et al. 2002; Rajkowska et al. 1999), anterior cingulate cortex (Cotter et al. 2001; Gittins and Harrison 2011), subgenual cortex (Ongur et al. 1998) and amygdala (Bowley et al. 2002). In white matter of postmortem human brain tissue and in rats subjected to chronic stress, the density of astrocytes and glial fibrillary acidic protein (GFAP)-positive area fraction were substantially reduced when compared with healthy controls (Rajkowska and Stockmeier 2013). Following exposure to different types of stress, GFAP expression and density of astrocytes were also reduced in grey matter of rodents exhibiting depressive behaviour (Braun et al. 2009; Czeh et al. 2006). In animal models of attention-deficit disorder and MDD, downregulation of classical astroglial markers such as glutamine synthetase, plasmalemmal glutamate transporters, aquaporin 4 and astroglia-specific connexins was reported (Barley et al. 2009; Bernard et al. 2011; Sequeira et al. 2009). Pharmacological inhibition of astroglial glutamate transporters (Bechtholt-Gompf et al. 2010) and gap junction connectivity (Sun et al. 2012) triggered anhedonia indicative of depression.

Impact of Antidepressants on Astrocytes

Increased awareness of astrocyte importance in regular brain function has provided fresh momentum to an old idea that astrocytes play a causative role in the pathogenesis of psychiatric disorders and can be utilized as cellular targets for antipsychotic drugs. Classic antidepressants (such as Li^+, valproic acid or fluoxetine) indeed affect astrocyte signalling cascades and modify expression of a variety of receptors and

transporters responsible for CNS homeostasis and support of synaptic transmission (Czeh and Di Benedetto 2013; Dong et al. 2015; Liu et al. 2015; Peng et al. 2018; Rivera and Butt 2019). Astroglial serotonin 5-HT_{2B} receptors interact with antidepressants belonging to serotonin specific reuptake inhibitors (SSRI) that include fluoxetine, citalopram, paroxetine, sertraline and fluvoxamine (Zhang et al. 2010). Fluoxetine and other SSRIs acting on astroglial 5-HT_{2B} receptors trigger Ca^{2+} signalling (Schipke et al. 2011) and transactivation of EGF receptor linked to MAPK/ERK and PI3K/AKT signalling cascades that modulate multiple homeostatic pathways including expression of glutamate transporters, glucose metabolism, astroglial secretion and activity of Na^{+}-H^{+} exchanger (Hertz et al. 2012, 2015; Liu et al. 2015; Peng et al. 2018; Ren et al. 2015). Besides SSRIs, other antidepressants also affect astrocyte function. Metabolic inhibition of astrocytes by intra-hippocampal injection of fluoroacetate prevents antidepressant action of imipramine (Iwata et al. 2011). Li^{+}, the oldest classical antidepressant, acting through astrocyte lysyl oxidase, encoded by LOX gene, profoundly affects astrocyte morphogenesis and proliferation (Rivera and Butt 2019). Electroconvulsive therapy, regarded as the last resort for the treatment of MDD (Li et al. 2020), upregulates GFAP expression that is generally suppressed in depressive disorders (Fujiki and Steward 1997; Kragh et al. 1993). Transcranial direct current stimulation triggers cortex-wide global elevation of cytosolic Ca^{2+} in astrocytes that is mediated by α1 adrenoreceptor activation and astroglia-specific $InsP_3$ receptors type 2 (Monai et al. 2016).

Ketamine: The Fastest Acting Antidepressant

Ketamine, (S)-(+) and (R)-(–)-2-(2-chlorophenyl)-2-(methylamino) cyclohexanone, is an arylcycloalkylamine structurally related to phencyclidine that is occasionally used as an anaesthetic in human and veterinary medicine. It also exerts analgesia and dysphoria and is sympathomimetic. Ketamine is quickly metabolized to norketamine and nordehydroketamine that appear in venous blood 10 and 30 min after administration. (S)-(+) and (R)-(–) enantiomers have similar pharmacokinetic profiles (Domino 2010). Since first clinical studies demonstrated that a single subanaesthetic dose of ketamine evokes rapid (within 2 h) and lasting (up to 2 weeks) antidepressant effect, ketamine generated substantial interest in psychiatry (Berman et al. 2000). The speed of antidepressant effect is in striking contrast to classic SSRI antidepressants that target monoamine system and typically require weeks to produce the therapeutic effect.

Ketamine binds to the phencyclidine-binding site of the NMDA receptor and blocks the ion flux through the receptor pore. (R)-(–) ketamine has an approximately fourfold smaller affinity for NMDA receptor than (S)-(+) ketamine and shows smaller negative psychotomimetic side effects when compared to (S)-(+) ketamine (Domino 2010); its antidepressant effect is seemingly more potent than of (S)-(+) ketamine (Yang et al. 2015). The antidepressant effect of ketamine outlasts the lifetime of the drug in the organism (Mion and Villevieille 2013) and indicates

that the molecular mechanism of ketamine effect extends beyond mere NMDA receptor antagonism. As other NMDA receptor antagonists do not exhibit antidepressant capabilities (Newport et al. 2015; Zanos et al. 2016), ketamine inevitably affects additional molecular targets besides NMDAR. Ketamine increases synaptogenesis, dendritic spine density, expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor and arborisation of astrocytes (Ardalan et al. 2017; Li et al. 2010; Maeng et al. 2008). The latter control membrane transport of glutamate and glucose, glial-to-neurone gap junction communication, cell volume and blood flow (Verkhratsky and Nedergaard 2018), and ketamine affects various aspects of astrocyte physiology (Lasic et al. 2016; Mitterauer 2012; Stenovec et al. 2016; Thrane et al. 2012; Wray et al. 2019).

Ketamine Increases Astrocyte cAMP and Alters Single Vesicle Interactions with the Plasmalemma

In protoplasmic astrocytes, cAMP plays a role in the establishment of arborised cell structure (Koyama et al. 1993; Schiweck et al. 2018; Won and Oh 2000) that creates territorial domain of an individual astrocyte (Bushong et al. 2002). Within this domain, astrocyte contacts up to 100,000 synapses (in rodents) through fine, submicrometre-sized processes (Halassa et al. 2007; Ogata and Kosaka 2002; Witcher et al. 2007). These processes and astrocyte-derived factors promote synaptogenesis (Pfrieger 2010) and influence synaptic activity (Fiacco et al. 2009; Nimmerjahn 2009; Perea et al. 2009; Santello and Volterra 2009; Theodosis et al. 2008). In the absence of G-protein-coupled receptor activation, ketamine induces a sustained increase in intracellular cAMP concentration ($[cAMP]_i$) in astrocytes (Fig. 1) (Lasic et al. 2016; Wray et al. 2019). This increase in $[cAMP]_i$ may attenuate delivery of vesicle-laden channels to the plasmalemma (Potokar et al. 2013; Stenovec et al. 2016, 2020) and modify luminal cargo release or uptake of extracellular molecules through altered fusion-pore structure (Lasic et al. 2016; Stenovec et al. 2016). In C6 glioma cells, ketamine facilitates cAMP signalling in a NMDA receptor-independent manner by affecting the translocation of $G_{\alpha s}$ from lipid rafts to non-raft membrane microdomains allowing increased functional coupling of $G_{\alpha s}$ and adenylyl cyclase. Ketamine subsequently increases phosphorylation of cAMP-response element-binding protein (CREB), which, in turn, increases the expression of BDNF (Wray et al. 2019) that has been widely implicated in the pathophysiology of MDD (Autry

Fig. 1 (continued) signal increase ($k = 2.2 \pm 0.6\%$/min). Ordinate on the right displays the values of $[cAMP]_i$ estimated from equation: $[cAMP]_i = EC_{50} \times ((R - R_{min})/(R_{max} - R))^{1/n}$ (Borner et al. 2011). (**c**) Mean amplitude (±SE; ΔFRET; left panel) and initial rate of the FRET signal change (ΔFRET/Δtime; right panel) in controls (white bars) and in astrocytes treated with ketamine (KM, black bars). Changes in the FRET signal are expressed as percentages of the initial values. Numbers above the error bars depict the number of cells analysed. Mann-Whitney U test: $^*P < 0.05$, $^{**}P < 0.01$. (Reproduced with permission from Lasic and colleagues (2016))

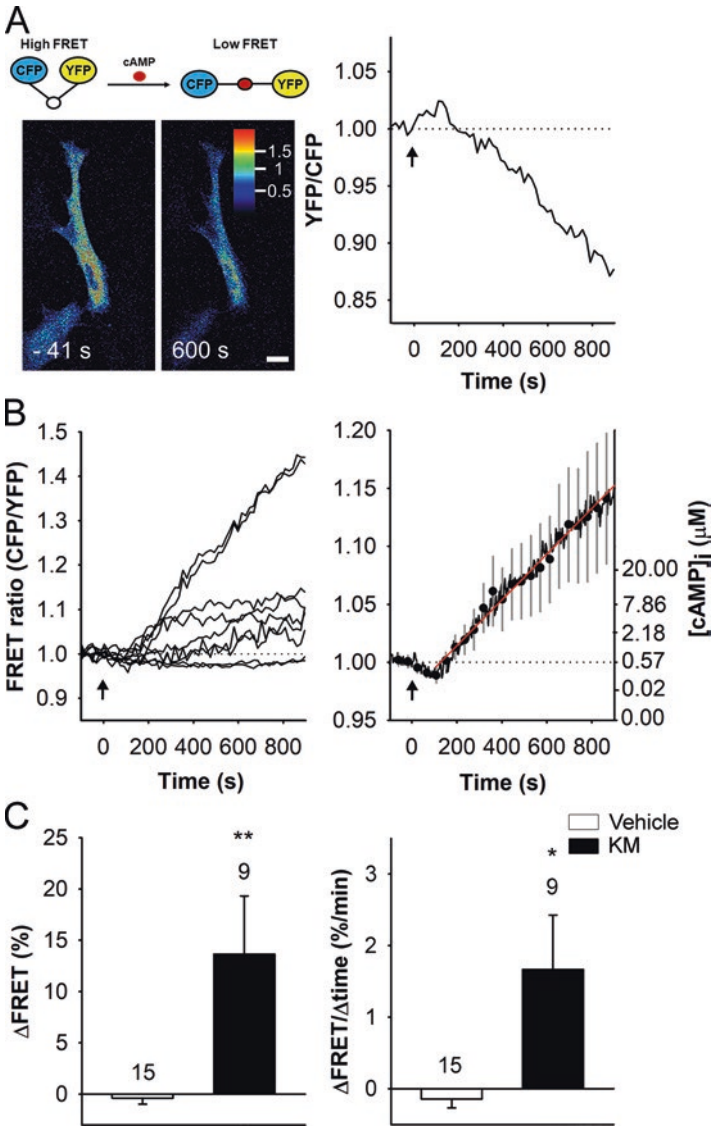

Fig. 1 Ketamine increases $[cAMP]_i$ in cultured rat astrocytes. (**a**) Schematic representation of FRET-based Epac1-camps nanosensor function (top) and pseudo-coloured FRET images of an astrocyte expressing the FRET-based nanosensor Epac1-camps before (−41 s) and after (+600 s) application of 25μM ketamine (bottom) and the corresponding normalized time-resolved trace of the Epac1-camps FRET signal (YFP/CFP; right). The pseudo-coloured scale indicates the YFP/CFP ratio values. Scale bar, 20μm. (**b**) Time-resolved (left panel) and the mean time-resolved (±SE; right panel) traces of the Epac1-camps FRET signal in astrocytes ($n = 9$) stimulated with ketamine at $t = 0$ s (black arrows). Data are expressed as the inverted FRET signal (CFP/YFP). Ketamine-evoked increase in the FRET signal reflects an increase in $[cAMP]_i$. The initial rate of change in $[cAMP]_i$ (red line; right panel) was determined by fitting the regression line to the FRET

and Monteggia 2012; Duman et al. 2016; Jiang and Salton 2013). Besides neurones, astrocytes also synthesize BDNF and are targeted by antidepressants (Autry and Monteggia 2012; Bjorkholm and Monteggia 2016; Hisaoka-Nakashima et al. 2016). In primary cortical astrocytic, but not in neuronal cultures, SSRI antidepressants fluoxetine and paroxetine, and the tricyclic antidepressants imipramine and amitriptyline upregulate the BDNF mRNA levels in a monoamine-independent manner (Allaman et al. 2011; Hisaoka-Nakashima et al. 2016; Kittel-Schneider et al. 2012; Musazzi et al. 2014; Takano et al. 2012), possibly through a direct effect on the extracellular signal-regulated kinase- and p38 mitogen-activated protein kinase-dependent signalling pathway. At single vesicle level, ketamine suppresses exocytotic release of BDNF from cultured rat astrocytes (Stenovec et al. 2016) and attenuates ATP-evoked increases in $[Ca^{2+}]_i$ in cultured cortical (Stenovec et al. 2016) and neocortical (Thrane et al. 2012) astrocytes in mice. Reduced vesicular release of BDNF and the diminished frequency of reversible and irreversible exocytotic events (Stenovec et al. 2016) can be explained by attenuation of ATP-evoked calcium signalling in ketamine-treated astrocytes. Ketamine may diminish stimulus-evoked Ca^{2+} signalling by modifying Ca^{2+} entry through TRP channels (Abdelhamid et al. 2014; Bahnasi et al. 2008), which contribute to the replenishment of the endoplasmic reticulum store (capacitive function) (Malarkey et al. 2008) and to the plateau phase of the Ca^{2+} transient (Verkhratsky et al. 2012). Moreover, ketamine disrupts synchronization of astrocytic slow inward currents presumably mediated by the extrasynaptic GluN1/GluN2B receptor activation and inhibits glutamate transmission from astrocytes to neurones (Zhang et al. 2019).

In clinically relevant concentrations, ketamine modulates interaction of single vesicles with the astrocyte plasmalemma by stabilizing a narrow fusion pore (Lasic et al. 2016). Low ketamine concentration of 0.25–2.5μM (Tassonyi et al. 2002) causes vesicles to lapse into a state of repetitive fusion pore opening and closing (Lasic et al. 2016). Flickering pore activity may hinder cargo discharge (Kreft et al. 2018) or uptake and/or vesicle recycling affecting retention of membrane receptors, transporters and ion channels at the astrocyte surface (Zorec et al. 2016). The mechanism(s) underlying flickering pore activity is/are still debated. As ketamine permeates membranes at physiological pH (Keiser et al. 2018) and accumulates inside acidified vesicles as a protonated weak base (Lester et al. 2015), it may directly affect the membranous pore (Jain et al. 1985) by electrostatically altering the anisotropicity of the pore (Kabaso et al. 2012). As ketamine principally inhibits endocytotic vesicle retrieval (Lasic et al. 2016), it could obstruct the uptake of BDNF into astrocytes (Bergami et al. 2008; Vignoli et al. 2016) and favour increased level of extracellular BDNF that is likelier to signal to nearby synapses and support long-term potentiation via sustained TrkB activation leading to enhancement of synaptic strength between neurones (Autry and Monteggia 2012; Duman et al. 2016; Jiang and Salton 2013).

Ketamine Induces Cholesterol Redistribution in the Astrocyte Plasmalemma

Synaptic transmission between neurones enables seamless operation of the central nervous system. Synaptic connectivity and synaptic function are regulated by perisynaptic astrocyte processes (Verkhratsky and Nedergaard 2014, 2018). Unless supported by astrocytes, cultured retinal ganglion neurones form few synapses that are functionally immature (Nagler et al. 2001; Pfrieger and Barres 1997; Ullian et al. 2001). Upon addition of astrocytes, the total number of synapses on neurones increases by sevenfold (Pfrieger and Barres 1997). As synapses formed in the presence of astrocytes are quickly lost after their removal, astrocyte-derived signals are also required to stabilize synapses (Ullian et al. 2001). One of the key synapse-promoting signals released by astrocytes to neurones is cholesterol (Mauch et al. 2001). In the brain, cholesterol derives almost entirely from in situ synthesis by brain cells (Dietschy and Turley 2001). As the appearance of most synapses in the developing brain temporally and spatially coincides with the development of astrocytes, synapse formation very likely depends on astrocyte-derived cholesterol (Ullian et al. 2001).

On the other side, postmortem studies in psychiatric patients (suffering from schizophrenia, bipolar disorder and MDD) revealed suspicious loss of astrocytes in brain regions important for mood, motivation and cognition (Bowley et al. 2002; Cotter et al. 2001, 2002; Gittins and Harrison 2011; Ongur et al. 1998; Rajkowska et al. 1999). The loss in glia cell numbers in animal models of depression and MDD patients or suicide victims (Rajkowska and Stockmeier 2013; Sanacora and Banasr 2013) is suggestive for hindered supply of astrocyte cholesterol to neurones that require cholesterol to build up axons, dendrites and synapses (Goritz et al. 2005; Pfenninger 2009) and to maintain functional synapses (Theodosis et al. 2008). Presynaptic vesicles with particularly high cholesterol content (40 mol%) and postsynaptic spines account for large amounts of neuronal membranes (Takamori et al. 2006). Neurones produce sufficient amount of cholesterol to survive and grow, yet they require astrocyte-derived cholesterol to form new synapse in abundance and to mature these synapses (Mauch et al. 2001). In ganglion neurones, the number of synapses and their activity (spontaneous and evoked) increases within 3 days after the addition of glia-conditioned medium or cholesterol (5μg/ml) to neuronal culture medium (Goritz et al. 2005).

Earlier in vitro studies indicated that soluble and contact-dependent astrocyte signals stimulate the formation of synapses in neurones from the hippocampus (Hama et al. 2004), retina (Mauch et al. 2001; Nagler et al. 2001; Ullian et al. 2001) and spinal cord (Peng et al. 2003), whereas a recent study (Lasic et al. 2019) revealed that ketamine instigates rapid redistribution of cholesterol in the plasmalemma of cortical astrocytes. Visible redistribution of cholesterol-enriched lipid rafts labelled with a fluorescent cholesterol-specific membrane-binding domain (D4) (Liu et al. 2017; Ohno-Iwashita et al. 1990) was observed already after 30 min ketamine treatment and indicated increase in D4-positive plasmalemmal domain density (Fig. 2).

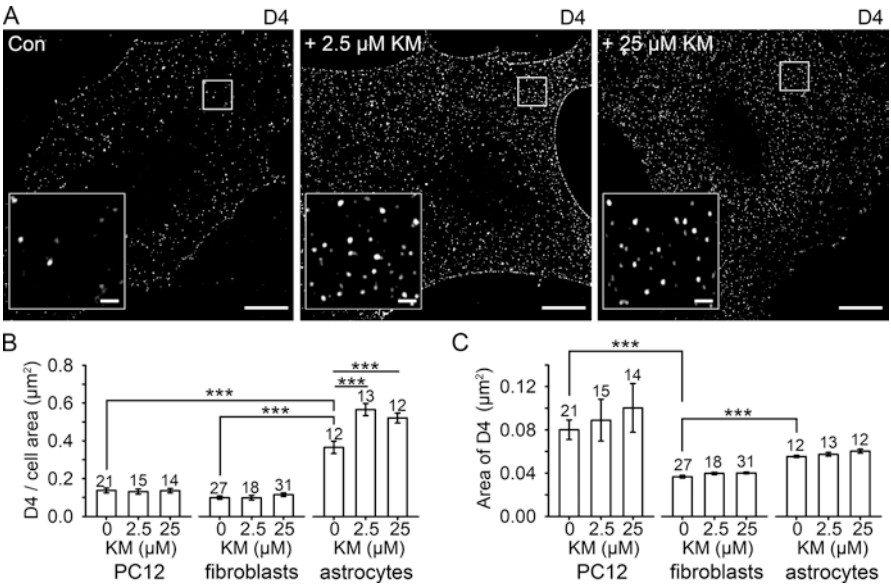

Fig. 2 Ketamine (KM) increases the surface density of cholesterol-rich plasmalemmal domains in astrocytes. (**a**) SIM images displaying mCherry-D4-labelling in non-treated controls (Con) and ketamine-treated astrocytes (2.5μM and 25μM KM, respectively). Insets show mCherry-D4 labelled domains at a higher magnification. Scale bar (inset), 10μm (1μm). (**b**) The density of the membrane cholesterol domains (the number of cholesterol domains (D4) normalised to the cell surface area) significantly increased in astrocytes after treatment with 2.5μM (0.57 ± 0.03 D4/μm^2) and 25μM KM (0.52 ± 0.03 D4/μm^2) when compared with controls (0.37 ± 0.03 D4/μm^2) (***$P < 0.001$, Holm-Sidak one-way ANOVA). Ketamine did not affect the density of cholesterol-rich domains in the PC12 cell line and fibroblasts. The density of the D4-positive domains was higher in astrocytes (0.37 ± 0.03 D4/μm^2) compared with PC12 cells (0.14 ± 0.01 D4/μm^2) and fibroblasts (0.10 ± 0.01 D4/μm^2) (***$P < 0.001$, Kruskal-Wallis test). (**c**) The average area of cholesterol-rich domains in vehicle-treated controls and in ketamine-treated cells (2.5 and 25μM) did not differ in the PC12 cell line, fibroblasts and astrocytes, but it differed between different cell types. The area of D4-positive domains was significantly higher in the PC12 cell line (0.080 ± 0.009μm^2) and astrocytes (0.056 ± 0.001μm^2) than in fibroblasts (0.037 ± 0.001μm^2) (***$P < 0.001$, Kruskal-Wallis test). The data in the graphs are reported as mean ± SEM. Numbers above the bars represent the number of cells analysed. (Reproduced with permission from Lasic and colleagues (2019))

As astrocytes promote maturation of synapses (Mazzanti and Haydon 2003; Nagler et al. 2001; Ullian et al. 2001) and maintain their structure and function (Slezak and Pfrieger 2003; Ullian et al. 2001), increased plasmalemmal cholesterol in ketamine treated astrocytes may transiently boost cholesterol flux to neurones and counteract the pathophysiological reduction in dendritic spine number and function of neurones in animal model of depression (Radley et al. 2006) or reduction in the number of synapses in MDD subjects (Kang et al. 2012). How exactly ketamine increases the density of plasmalemmal cholesterol-enriched domains is still unclear. As an overall increase in astrocyte cholesterol production is unlikely (Kritchevsky et al.

1976; Saranteas et al. 2005), an alternative explanation is needed. In astrocytes, sub-anaesthetic ketamine dose evokes flickering activity of narrow fusion pore that hinders vesicle retrieval (Lasic et al. 2016). Prolonged flickering activity may contribute to an increased density of plasmalemmal cholesterol, as cholesterol-enriched domains are less effectively internalized via vesicle endocytosis. Cholesterol enrichment in the outer leaflet of the astrocyte plasmalemma (Lasic et al. 2019) may thus result in an enhanced flux of cholesterol to neurons, where it is required for changes in synaptic plasticity (Goritz et al. 2005), leading to sustained strengthening of excitatory synapses necessary for improvement of depressive phenotype (Zanos and Gould 2018). Such proposal, however, requires further experimental study.

Ketamine Attenuates Mobility of Vesicles Delivering Kir4.1

As our lives are shaped by numerous opposing forces, our brain is equipped with the similarly opposing systems guiding our actions and influencing our mood. Neurones in the mesolimbic system promote reward-seeking behaviour, whereas neurones in the lateral habenula (LHb) suppress this behaviour (Howe and Kenny 2018). In LHb neurones, a distinctive pattern of burst firing is causally associated with depressive phenotype and reduced extracellular concentration of K^+ ($[K^+]_o$) (Cui et al. 2018). One of the major conduits for the movement of K^+ between the extracellular space and astrocytes is an inward-rectifier K^+ channel termed $K_{ir}4.1$ (Breslin et al. 2018; Nwaobi et al. 2016). In rat models of depression, this channel was found to be upregulated at the transcript, protein and functional levels (Cui et al. 2018). When overexpressed, $K_{ir}4.1$ hyperpolarises membrane potential and causes burst firing of LHb neurones, which results in depressive behaviour. Decrease in $[K^+]_o$ thus mimics the depressive phenotype. Conversely, disruption of $K_{ir}4.1$ function by viral-mediated knockdown or expression of dominant negative construct depolarised membrane potential and causes tonic firing of LHb neurones. As depression-associated burst firing in neurones is favoured by overexpressed astrocyte $K_{ir}4.1$ lowering $[K^+]_o$ (Yang et al. 2018), modulating $K_{ir}4.1$ activity in the brain areas involved in the regulation of mood and motivation might be a way to treat psychiatric disorders. Despite recent studies demonstrated that ketamine infusion into LHb blocks burst firing and causes rapid antidepressant effects in depression-prone rats, none of them addressed the possibility that ketamine also alters trafficking and/or

Fig. 3 (continued) (top; Con) or treated with 2.5μM (middle) or 25μM (bottom) ketamine (KM). The mask images (white, right) display co-localized pixels. Scale bars, 20μm. (**b**) Ketamine treatment diminishes directional mobility of $K_{ir}4.1$-EGFP vesicles. (**c**) Co-localization (mean ± SE; %) of FM4–64 versus Kir4.1-EGFP fluorescence indicates diminished localization of $K_{ir}4.1$-EGFP at plasmalemma in astrocytes treated with 2.5 or 25μM ketamine (KM). The numbers above the top and bottom of the bars indicate the number of cells (**b**, **c**) and vesicles (**b**) analysed, respectively. *$P < 0.05$ (ANOVA on ranks followed by Dunn's test; **b**, **c**). (Reproduced with permission from Stenovec and colleagues (2020))

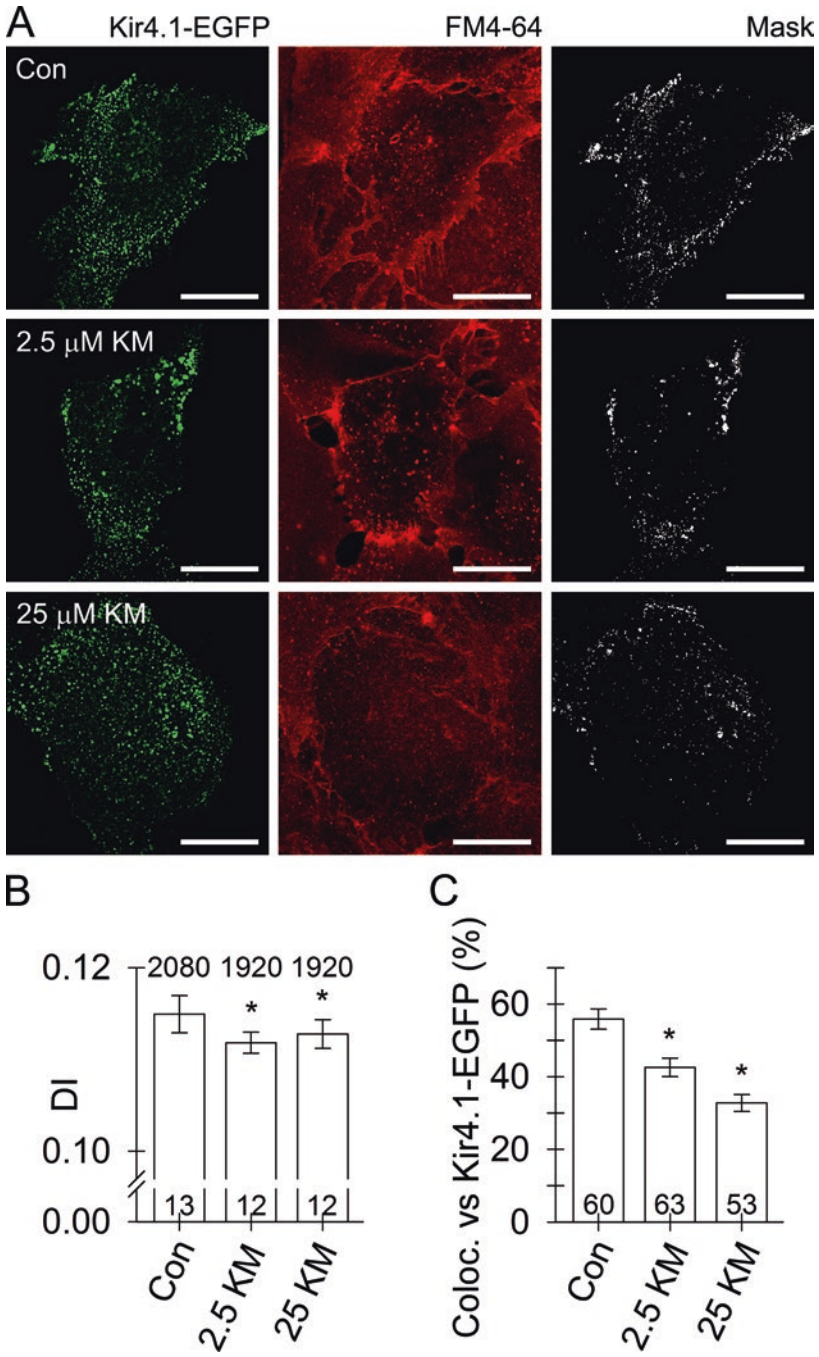

Fig. 3 Ketamine reduces mobility of $K_{ir}4.1$ vesicles and surface density of $K_{ir}4.1$ in astrocytes. (**a**) Confocal images of transfected astrocytes expressing $K_{ir}4.1$-EGFP vesicles (green, left) and labelled with the membrane styryl dye FM4–64 (red, middle) that were not treated with ketamine

surface density of $K_{ir}4.1$ or even inhibits this channel. Notably, $K_{ir}4.1$ is reversibly inhibited by antidepressants of the tricyclic and SSRI class, such as nortriptyline and fluoxetine (Furutani et al. 2009; Ohno et al. 2007; Su et al. 2007). Whether ketamine also inhibits $K_{ir}4.1$ function is currently unknown. Ketamine, however, reduces cytoplasmic mobility of vesicles carrying the inward-rectifier potassium channel ($K_{ir}4.1$) and diminishes $K_{ir}4.1$ density at astrocyte surface (Fig. 3; Stenovec et al. 2020), which may raise extracellular K^+ concentration and alleviate depressive behaviour in animal models of depression (Cui et al. 2018) and possibly also in humans (Berman et al. 2000).

Seemingly diverse but not mutually exclusive mechanisms may act synergistically to evoke changes in synaptic plasticity leading to sustained strengthening of excitatory synapses necessary for antidepressant effect of ketamine. Studies in astrocytes may provide alternative ground for the development of novel astrocyte-targeted therapeutic drugs suitable for the treatment of psychiatric disorders.

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Epilogue

Neuropsychiatric diseases have been almost universally considered from the neuron-centric point of view, with neurons being the central cellular element of pathological process. However, brain homeostasis lies at the fulcrum of healthy brain function, and its compromise invariably results in disease. Astrocytes control homeostasis of the nervous system at organ (establishment and maintenance of the blood-brain barrier), tissue (creating micro-architecture of the nervous tissue), cell (providing for neuron- and glio-genesis), and molecular (by controlling ion and neurotransmitter homeostasis) levels. These glial cells are also central for regulating nervous system microcirculation and neuronal energy support. Astrocytes are also capable of gliotransmission, i.e., releasing transmitters to communicate among themselves (homocellular signaling) and with other cell types (heterocellular signaling) residing in the nervous system. Astrocytic excitation underlying cell-cell signaling relies on excitability of these glial cells based on variations of intracellular calcium (and other) ion levels rather than electrical excitability as seen in neurons. Finally, astrocytes contribute to neural defense, and every lesion to the nervous tissue initiates evolutionary conserved and universal glial reaction manifested by reactive astrogliosis.

Multiple roles of astrocytes, which determine the progression and outcome of neuropsychiatric diseases, are emerging, and it is becoming clear that astrocytes are involved in various aspects of disease initiation, progression, and resolution. In this edited volume, we aimed to integrate the body of information that has accumulated in recent years revealing the active role of astrocytes in neuropsychiatric pathology. Understanding the roles of astrocytes in pathology will provide new targets for medical intervention and aid in the development of much needed therapeutics. By no means have we claimed that astrocytes are the sole cell type underlying psychiatric disorders. That would be a simple-minded act especially when considering the multifactorial nature of psychiatric disorders. Quite contrary, we firmly support the notion that all neural cells, as well as cells of vasculature (the neurovascular unit), with all their morpho-functional and dynamic interactions and signaling cascades,

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contribute to psychiatrist pathologies. Furthermore, we are also in support of an even more holistic vision in which the brain's interaction with other body systems, such as endocrine, immune, lymphatic, gastrointestinal (e.g., the gut-brain axis), and others, could contribute to etiology and pathogenesis of psychiatric disorders.

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