

Review

Recent advances in (patho)physiology of astroglia

Alexei VERKHRATSKY^{1,2,*}, Vladimir PARPURA³

¹Faculty of Life Sciences, The University of Manchester, Manchester, UK; ²IKERBASQUE, Basque Foundation for Science, 48011, Bilbao, Spain; ³Department of Neurobiology, Center for Glial Biology in Medicine, Civitan International Research Center, Atomic Force Microscopy & Nanotechnology Laboratories, and Evelyn F McKnight Brain Institute, University of Alabama, Birmingham, USA

Our view of astrocytes in the operation of the brain is changing dramatically over the last 3 decades. Astroglial calcium excitability controls the release of gliotransmitters, which can occur at the tripartite synapse. Astrocytes not only modulate synaptic transmission by releasing and taking up transmitters, but also receiving neuronal signals that act upon astrocytic plasma membrane receptors. This process represents the bidirectional neurone-glia communication. Additionally, astrocytes play role in the regulation of blood flow as well as ion and water homeostasis. Many of the brain dysfunctions are primary astropathies, including hepatic encephalopathy and Alexander disease, while other brain malfunctions, such as epilepsy and Alzheimer disease, may have substantial astrocytic contribution. Thus, these star-shaped cells by their roles in (patho)physiology of the brain seem to live up to the expectation one can have from their given name – astrocyte.

Keywords: neuroglia; astrocyte; gliotransmission; neuropathology; neurodegeneration

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History of glial research

At the dawn of neuroscience all neural cells were equal. Indeed early neuroanatomists were describing both neuronal and glial elements of the nervous system without assigning them special priorities. The first descriptions of neurones were made by Christian Gottfried EHRENBURG (1836), by Johann Evangelista PURKINJE (1835–1837), and by Gustav Gabriel VALENTIN (1836). At the very same time Robert REMAK discovered glial sheath surrounding axons, and in 1850-ies Heinrich MÜLLER, Max SCHULZE and Karl BERGMANN made first detailed investigations of glial cells in retina and in cerebellum. The concept of glia as a connective tissue component of the CNS was introduced by Rudolf VIRCHOW, who also introduced the idea of supportive role of neuroglia, which is the “substance... which lies between the proper nervous parts, holds them together and gives the whole its form in a greater or less degree”^[1]. Very soon after Virchow however, the cellular nature of glia was firmly established and many types of glial cells were revealed and minutely described (for more detailed account on the history of glial research see^[2,3]). Initially all glial cells in the CNS were classified as “spider” or “stellate” cells. The term “astrocyte” was introduced in 1891

by Michael von LENHOSSEK^[4]; very soon after Rudolf Albert von KÖLLIKER and William Lloyd ANDRIEZEN^[5,6] further classified astroglia into protoplasmic and fibrous astrocytes located in the grey and in the white matter respectively. The second and third neuroglial elements, represented by oligodendrocytes and microglia were identified by Pio del RÍO-HORTEGA in 1920-ies^[7–9].

By the beginning of 20-ies century the preponderance of glia in the human CNS was universally accepted; similarly the great morphological variety of astrocytes was widely documented^[10]. Numerous hypotheses were also proposed to understand the function of neuroglia. Some of these hypotheses regarded glia as completely passive insulators (Pedro Ramon Y CAJAL), some highlighted the role of neuroglia in metabolic support of nerve elements (Camillo GOLGI), or proposed that that these cells may release substances into the blood, acting like an endocrine gland (Jean NAGEOTTE), and at least one hypothesis regarded neuroglia as a major regulator of information processing in the brain (Carl Ludwig SCHLEICH). All this hypothesising however came to an abrupt end with the final victory of the neuronal doctrine (that occurred at the beginning of 20-ies century) that regarded synaptically connected neuronal networks as a sole substrate for brain functional activity, leaving neuroglia in the position of passive supporters. As a result, the glial research remained dormant for almost three quarters of a century. In the last 3

* To whom correspondence should be addressed.
E-mail alex.verkhratsky@manchester.ac.uk
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decades however, this changed dramatically and many exciting discoveries elevated glia to a substantially more dignified position. In this essay we attempt to provide a concise account of major advances in the physiology and pathophysiology of astroglia.

Physiology of astroglia

The astrocytes, which are the most numerous cells in the human brain, have many functions (Table 1). First and foremost, astrocytes represent the main cellular element of homeostatic system, which is responsible for all aspects of metabolic support, nutrition, control of ion and neurotransmitter environment, regulation of brain-blood barrier and defence of the central nervous system^[11]. In addition, astrocytes express a multitude of signalling cascades, are endowed with trans-cellular communication routes represented by gap junctions and are able to release a wide array of gliotransmitters via several regulated pathways. This complex signalling machinery may involve astroglia in a variety of information processing routines existing in the CNS and make astrocytes indispensable elements in shaping higher cognitive functions of the brain.

Astrocytes shape the grey matter

Astroglia define the micro-architecture of the grey matter by

Table 1. Functions of astroglial cells (modified from^[14]).

Astroglial functions	
Developmental	Regulation of neuro- and gliogenesis – astroglia are stem elements of the CNS Neuronal path finding Regulation of synaptogenesis
Structural	Astroglia divide the grey matter into independent territories and form neuro-vascular units Astrocytes form anatomically segregated syncytia and integrate other neural cells into this syncytium Formation of the glial-vascular interface and regulation of blood-brain barrier
Metabolic	Regulation of cerebral microcirculation Providing energy substrates for neurones through glucose-lactate shuttle
Homeostatic	Regulation of extracellular ion concentrations; in particular sequestration and redistribution of K ⁺ following fluctuations associated with neuronal activity Regulation of extracellular pH Homeostasis of neurotransmitters and specifically glutamate Brain water homeostasis
Signalling	Modulation of synaptic transmission and synaptic plasticity Release of gliotransmitters Long-range signalling within the glial syncytium Integration of neuronal-glia networks

dividing the latter into relatively independent structural units. The protoplasmic astrocytes occupy defined territories and create the micro-anatomical domains within the limits of the arborisation of their processes^[12-16] (Figure 1). Astrocytes have extensive morphological interactions with neurones within their individual domains. For instance, one astrocyte may contact 4 to 8 neurones and surround ~300 to 600 neuronal dendrites^[17] in the cortex of adult mice. In the hippocampus astrocytes are prolifically in contact with synapses. In adult rats, one astrocyte is estimated to contact ~140 000 synapses in the CA1 area^[13]. These individual astroglial domains are further integrated into astroglial syncytia through gap junctions, mainly localised on the peripheral processes of astroglial cells. These astroglial syncytia form the main pathway for inter-glia communications^[18]. The astroglial syncytia can also be anatomically segregated because they are formed within defined anatomical structures, for example in individual barrels of the somatosensory cortex^[19]. It should be noted, however, that the extent of gap-junctional connectivity between glial cells greatly varies between different regions of the brain, or even within a region, *eg*, within hippocampus^[20].

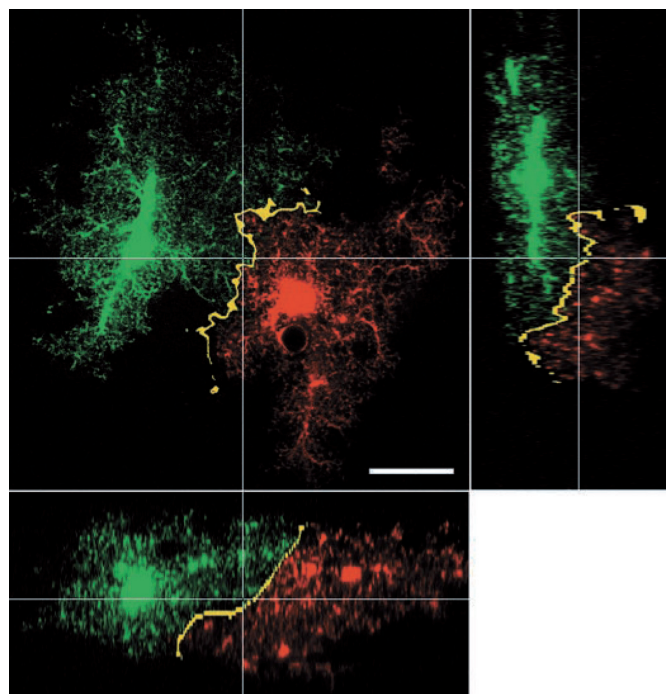


Figure 1. The protoplasmic astrocytes occupy defined territories within the CNS. Two adjacent astrocytes create their micro-anatomical domains (green and red). Only at the cells' peripheries do their processes overlap (yellow). Images represent x-y (large), x-z (bottom), and y-z (right) projections. Scale bar, 20 μ m. Reprinted, with permission from^[13] and the *Journal of Neuroscience* (Copyright 2002 by the Society for Neuroscience).

Astrocytes form communication “channels” with nearby neurones

Astrocytes can listen and talk to neurones via transmitter release^[21]. This is because of the intimate structural relation-

ship between these neural cells referred to as the tripartite synapse, whereby neuronal pre- and post-synaptic elements are wrapped by glial cell processes (Figure 2A). It is at the tripartite synapse where neurotransmitter released via synaptic transmission signals to adjacent glial cells and vice versa, astrocytic processes at the tripartite synapses possess gliotransmitter (often the same chemical as neurotransmitter, *eg*, glutamate) vesicles (Figure 2B) and by releasing it can modulate synaptic transmission and plasticity^[22]. Tripartite synapses are ubiquitously present throughout CNS. In the stratum radiatum of hippocampal CA1 region, 57% of the synapses formed between Schaffer collaterals and CA1 pyramidal neurones are in contact with astrocytes^[23]. However, the degree of synaptic coverage by glia is a dynamic process, as best described in the magnocellular hypothalamo-neurohypophysial system^[24].

Neurone-glia signalling can also occur through direct synapse-like connections synaptoids, ectopic sites at pre-synaptic terminals or even *bona fide* synaptic contacts (Figure 2C–2E). Thus, neuroglia are capable of responding to neuronal activity

at various levels/modes of neurotransmitter release including single action potential driven release as well as asynchronous quantal release.

Synaptoid contacts occur where axonal projections end on glial cells without notable presence of post-synaptic differentiation (PSD) on glia (Figure 2C). Such direct synapse-like contacts have been described in pituitary cells, specialized astrocytic cells, where stimulation of neuronal terminals caused γ -amino butyric acid (GABA) and dopamine mediated depolarizations of pituitary cells *in situ*^[25]. Synaptoids also exist on septohippocampal astrocytes formed by inputs from norepinephrine terminals^[26].

Bergmann glia, an astroglial cell found in the cerebellum, can receive inputs from climbing and parallel fibres *in situ*^[27]. Here, exocytosis of glutamate occurring at active zones excites Purkinje cells, while ectopic exocytotic glutamate release is used for signalling to Bergmann glia. Naturally, ectopic release sites are defined as release sites outside of the active zones of the presynaptic terminals (Figure 2D).

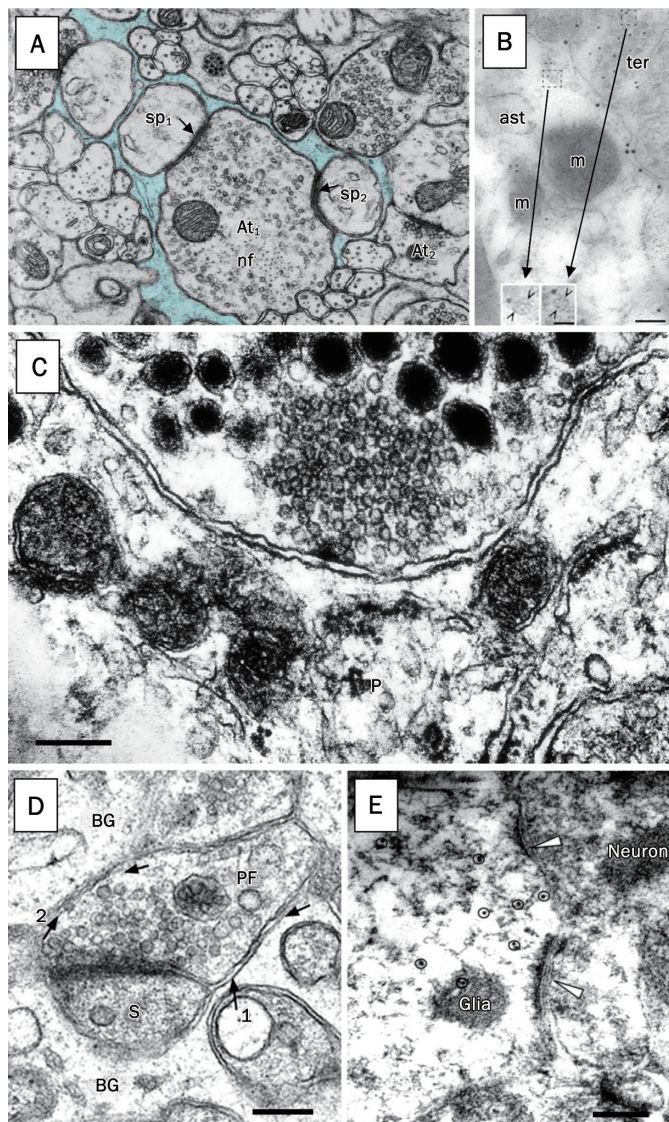


Figure 2. Types of contacts between neuronal terminals and astroglia. (A) An electron micrograph demonstrates the tripartite synapse. The cytoplasm of an astrocyte (blue) contacts axon terminals (At) forming synapses onto spines. Two synapses (sp_1 and sp_2 ; arrows) are wrapped by the astrocyte, while two other synapses (at_1 and at_2) are in close apposition to the astrocyte; nf, neurofilaments. (B) Glutamatergic vesicles at the putative tripartite synapse. Immuno-electron micrograph of vesicular glutamate transporter 1 (VGLUT1) (small gold particles) in astrocytic process (ast) identified by GLT/GLAST labelling (large gold particles). VGLUT1 positive vesicles (insets, open arrowheads) in an astrocyte and in the adjacent neuronal terminal (ter) have similar appearances; m, mitochondria. (C) Neurosecretory axon containing both dense core and clear secretory vesicles making a synaptoid contact with a pituitary astrocyte (P). The post-synaptic membrane differentiations are completely absent on the astrocyte apposing the presynaptic terminal. (D) Parallel fibre terminal (PF) is making a synapse on a dendritic spine (S) of a Purkinje neuron. Close appositions of Bergmann glia (BG) and PF membranes contain extracellular electron dense material (arrows, 1 and 2). Synaptic vesicles are morphologically docked to the presynaptic differentiations and close to the presynaptic membrane facing the BG. (E) Synaptic structures with typical neuronal synaptic terminals containing vesicles in contact (arrowheads) the EGFP/GFAP-positive glial cells labelled using indirect immunocytochemistry with anti-GFP and secondary antibody conjugated to gold particles (circles). Note postsynaptic densities in glial elements. Scale bars, 100 nm in B (50 nm inset), 330 nm in C, 100 nm in D, and 250 nm in E. Micrograph in A is modified from^[111] and reprinted from^[24], with permission from American Physiological Society. Micrograph in B is adapted by permission from Macmillan Publishers Ltd: Nature Neuroscience^[112], copyright 2004. Micrograph in C courtesy of the late Dr Glenn I. Hatton, University of California Riverside. D is reprinted from^[27], with permission from the *Journal of Neuroscience* (Copyright 2005 by the Society for Neuroscience). E is reprinted from^[29], with permission from the *Company of Biologists Ltd*.

Direct glutamatergic and GABAergic synapses on glial cells were observed in the hippocampus. Such synapses are formed on glial cells expressing the proteoglycan NG2, and hence regarded as oligodendrocyte precursor cells (OPCs)^[28] or on a subset of cells displaying the astrocytic marker glial-fibrillary acidic protein (GFAP) termed GluR cells^[29]. However, GluRs not only co-express common astrocytic markers S-100 β and GFAP, but also the proteoglycan NG2, and have transcripts for mainly neuronal excitatory amino acid carrier 1. Consequently, they do not match a definition of the “classical” astrocyte. Nonetheless, at the ultrastructural level, neuronal inputs onto GluR astroglial cells show all the morphological characteristics of chemical synapses, having the typical features of the neuronal pre-synaptic terminal with apposing PSDs in postsynaptic glial element (Figure 2E).

The existence of multiple structures mediating the transfer of information from neurones to glial cells using spillover, synaptoid, ectopic sites, and direct chemical synapses suggest a high level of complexity and specificity in neurone-glia signalling.

Astrocytes express “excitable” molecules

The seminal discovery of ionotropic glutamate receptors in neuroglia was made in 1984, when it was found that externally applied excitatory amino acids (glutamate and aspartate) depolarised astrocytes and oligodendrocytes maintained in cell culture^[30, 31]. In the next decade the wide variety of both neurotransmitter receptors and ion channels was discovered and characterised in astrocytes; in fact the astroglia was found to express virtually every type of ion channel and/or receptor present in the nervous system^[32, 33].

The receptors expression in glial cells *in vivo* is tightly controlled and astrocytes from different brain regions have very distinct complement of receptors. Often the receptor patterns expressed by astroglia match the receptors present in their immediate neuronal neighbourhood. For example Bergman glial cells and their intimate associates, Purkinje neurones, express receptors for adrenalin, histamine, glutamate, GABA and adenosine 5'-triphosphate (ATP), these receptors being congruent to the neurotransmitters released in this anatomical region^[34-36].

The most widespread receptors in astroglia are represented by glutamate receptors and purinoceptors. Majority of astroglial cells throughout the brain express metabotropic glutamate receptors that initiate Ca²⁺ signalling through phospholipase C/InsP₃-mediated Ca²⁺ release from the ER^[36]. The main astroglial ionotropic glutamate receptors is of AMPA-type, which often is expressed in Ca²⁺-permeable form^[32, 33]. Cortical astrocytes express NMDA receptors of specific “glial” variety characterised by an absence of Mg²⁺ block^[37, 38]. Through activation of their glutamatergic receptors astrocytes are able to “sense” synaptic transmission^[36].

The purinoceptors and purinergic signalling system is of specific importance for neuroglia, because virtually every type of glial cell does have sensitivity to ATP or adenosine^[39]. The reason probably lies in the ancient evolutionary roots of

the purinergic signalling system that from the very beginning of evolution has been employed as a main “warning” or “danger” signaller^[40, 41]; the neuroglia being the defender of the nervous system inherited this sensitivity to purines. The astroglial cells express both P1 (adenosine) and P2 (ATP and other nucleotides) receptors (Table 2). The metabotropic P2Y receptors are particularly abundant in astrocytes; the P2Y₁, P2Y₂, and P2Y₆ subtypes being largely expressed^[39]. Expression of ionotropic purinoceptors is much less explored; so far a specific expression of P2X_{1/5} heteromeric receptors was demonstrated in cortical astroglia^[42]. The P2X_{1/5} receptors are distinguished by extraordinary high sensitivity to ATP (EC₅₀ about 50 nmol/L) and absence of desensitisation. These peculiarities make the perfect sensor to monitor the ambient ATP fluctuation in the brain interstitium. There are some indications of astroglial expression of P2X₇ receptors^[43, 44], although these latter are probably relevant for pathological processes as various insults to the brain trigger significant up-regulation of P2X₇ expression in astrocytes^[39].

Table 2. Mammalian purine/pyrimidine receptors expression in the brain/astrocytes and their agonists.

Receptor	Agonist(s)	Brain	Astrocyte
(P1)A _{1,2A,2B,3}	Adenosine	+	+
P2X ₁₋₇	ATP (except P2X ₆) [*]	+	+
P2Y ₁	ADP>ATP	+	+
P2Y ₂	UTP=ATP	+	+
P2Y ₄	UTP≥ATP	+	+
P2Y ₆	UDP>UTP>ATP	+	+
P2Y ₁₁	ATP	+	
P2Y ₁₂	ADP>ATP	+	+
P2Y ₁₃	ADP>ATP	+	
P2Y ₁₄	UDP-glucose	+	+

Receptor families: P1, adenosine; P2 for ATP and ADP, P2X are ionotropic, P2Y are metabotropic. ^{*}P2X₆ does not form a homodimer. P2Y₅, P2Y₇, P2Y₉, P2Y₁₀ do not show responses to nucleotides. P2Y₃ is an avian ortholog of P2Y₆. P2Y₈ from *Xenopus laevis* shows high homology to mammalian P2Y₂ and P2Y₄.

Calcium excitability of astroglia

Despite the widespread expression of excitable molecules in astroglial plasma membrane, these cells remain electrically non-excitable because high density of K⁺ channels precludes regenerative depolarisation and action potential generation. Nonetheless astrocytes employ intracellular endomembrane as an excitable media (Figure 3). The endomembrane form the endoplasmic reticulum (ER) that provides for many levels of intracellular signalling and integration, being in particular the main dynamic intracellular Ca²⁺ store^[45, 46]. The ER is able to accumulate large amounts of Ca²⁺ via the activity of sarco(endo)plasmic reticulum Ca²⁺ ATPases, SERCAs; the intra-ER free Ca²⁺ concentration is comparable with extracellular free Ca²⁺, being in the range of 400–800 μ mol/L^[47, 48]. The

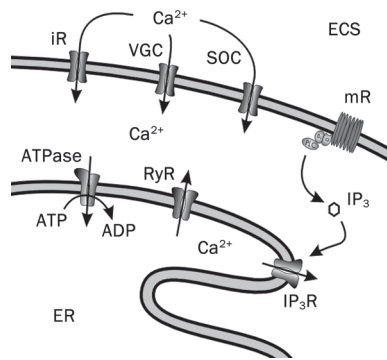


Figure 3. Ca^{2+} excitability of astrocytes. A drawing of sources of Ca^{2+} for cytosolic Ca^{2+} increase. Cytosolic Ca^{2+} signalling results from the entry of Ca^{2+} from the extracellular space (ECS) through ionotropic receptors (iR), voltage-gated channels (VGC) or store-operated channels (SOC). The intracellular source of Ca^{2+} is available from the endoplasmic reticulum (ER) intracellular stores that possess ryanodine and IP_3 receptors (RyR and IP_3R). IP_3R can be stimulated via activation of metabotropic receptors (mR). Modified from^[113].

ER membrane also carries intracellular Ca^{2+} channels (the Ca^{2+} -gated Ca^{2+} channels also known as ryanodine receptors and inositol (1,4,5)-trisphosphate (IP_3)-gated Ca^{2+} channels or IP_3 receptors), which, upon physiological stimulation, produce Ca^{2+} release^[49] (Figure 3). Depleted stores are replenished by SERCA pumps from cytosol, while the ultimate source for this ion is the extracellular space and store-operated Ca^{2+} entry (SOCE) to cytoplasm (Figure 3); molecularly SOCE channels in astrocytes most likely belong to the family of transient receptor potential channels^[50]. In addition to SOCE, Ca^{2+} entry across the plasma membrane involves a variety of other channels and/or receptors permeable to Ca^{2+} ^[33, 36] (Figure 3). Additionally, mitochondria act as a source/sink of cytosolic Ca^{2+} ^[51]. Both SERCA pumps and intracellular Ca^{2+} channels are subject to several feedback regulation cascades by cytosolic and intra-ER Ca^{2+} ^[52], which together with internal continuity of the ER lumen^[53, 54] allow the development of propagating wave of channels opening following local stimulation. This propagating wave of activation of ER Ca^{2+} channels forms glial excitability and underlie long-range signalling in glial syncytia manifested by propagating Ca^{2+} waves^[55].

Astrocytes release gliotransmitters

Gliotransmitter is a chemical released from glial cells classified based on a working set of criteria: (i) synthesis by and/or storage in glia; (ii) regulated release triggered by physiological and/or pathological stimuli; (iii) activation of rapid (milliseconds to seconds) responses in neighbouring cells; (iv) a role in (patho)physiological processes^[56]. Since the first demonstration of the release of GABA from glial cells in superior cervical ganglia^[57] and taurine from primary cultured astrocytes^[58], there has been an ongoing mission for determining and understanding of mechanisms and conditions that underlie gliotransmitter release. Generally, gliotransmitters can be released from astrocytes by several different mechanisms^[56]:

(i) through channels like anion channel opening induced by cell swelling, release through unpaired connexons, hemichannels, on the cell surface and ionotropic purinergic receptors; (ii) through transporters such as reversal of uptake by plasma membrane excitatory amino acid transporters, exchange via the cystine-glutamate antiporter or organic anion transporters; (iii) through Ca^{2+} -dependent exocytosis. Arbitrary, gliotransmitters can be divided into two general groups: (i) amino acids and their derivatives, such as glutamate, aspartate, homeocysteic acid, D-serine, GABA and taurine; (ii) nucleotides and their derivatives, like ATP, uridine 5'-triphosphate (UTP), adenosine and uridine diphosphate-glucose (UDP-glucose). We briefly outline mechanisms and conditions underlying the release of the gliotransmitter glutamate in chronological order of their discoveries (Figure 4).

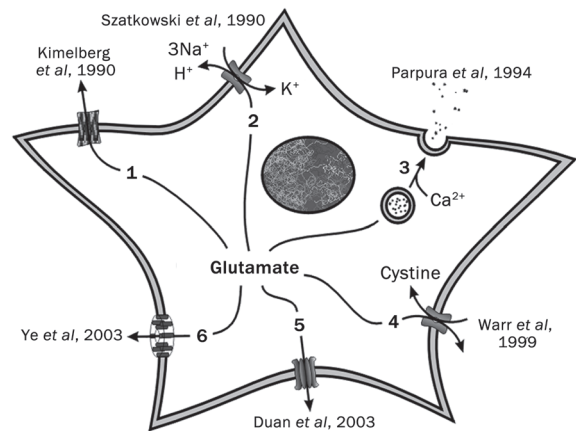


Figure 4. Glutamate release mechanisms in astrocytes. The six known mechanisms in are listed in the order of their discoveries along with original references: 1) swelling-induced opening of volume-regulated anion channels^[59]; 2) reverse operation of excitatory amino acid transporters^[60]; 3) Ca^{2+} -dependent exocytosis^[61]; 4) the cystine-glutamate exchanger^[67]; 5) connexon hemichannels^[69]; and 6) the P2X₇ receptor^[70]. Modified from^[113].

Swelling/anion channels

Under hypo-osmotic conditions, such as those occurring during ischemia, most cells experience swelling and can compensate for this volume increase by opening volume-regulated anion channels. These channels are permeable to inorganic and small organic anions, including the amino acids taurine, aspartate and glutamate, all of which have been demonstrated to be released from astrocytes stimulated with hypoosmotic media to induce swelling^[59] (Figure 4, mechanism 1).

Reverse operation of glutamate transporters

An important function of astrocytes is continuous control of extracellular glutamate concentration that is accomplished through the use of the plasma membrane excitatory amino acid transporters (see below). Normally, concentration gradients favour the transport of glutamate into astrocytes. During extreme situations, such as ischemia or metabolic blockade,

electro-chemical gradients can favour transporters to operate in reverse mode resulting in release of glutamate out of astrocytes^[60] (Figure 4, mechanism 2).

Ca²⁺-dependent exocytosis

Regulated exocytosis is a process whereby the fusion of vesicular and plasma membranes result in the release of chemical transmitters which are then used for communication between various cells. It is an evolutionary trait of eukaryotic cells, with the majority of ~200 cell types present in the human body performing it. Indeed, it has been demonstrated that astrocytes can release glutamate in Ca²⁺-dependent manner^[61] (Figure 4, mechanism 3). Astrocytic secretory machinery includes the presence of vesicular structures as well as various endo/exocytotic proteins^[62]. Addition of vesicular membranes to the plasma membrane can be recorded as an increased cell capacitance with concomitant occurrence of glutamate release^[63]. The cytosolic Ca²⁺ concentrations necessary and sufficient for glutamate release are likely to occur physiologically^[56]. Some of the functional consequences of vesicular release from astrocytes are evident in the modulation of spontaneous and evoked synaptic transmission as well as synaptic plasticity^[56]. There is also evidence that exocytotic release of ATP from astrocytes^[64], that extracellularly converts to adenosine, plays a role in sleep^[65].

Cystine-glutamate exchanger

Cystine uptake in astrocytes is important for the production of the antioxidant, glutathione. It can occur via two known systems (X_{AG}⁻ and x_c⁻) located on the plasma membrane. The majority of exchangers in the brain are localised in glial cells^[66]. The x_c⁻ system, which functions by importing cystine in exchange for glutamate, provides a pathway for glutamate release from astrocytes^[67] (Figure 4, mechanism 4). This glutamate release was associated with the modulation of synaptic transmission and the expression of animal behaviour related to addiction^[56].

Connexons

Gap junction channels are pores formed by the joining of two connexons ("hemichannels") each on juxtaposing plasma membranes of adjacent cells. Unpaired connexons have been discovered to be able to act as functional hemichannels, capable of opening to the external space^[68]. Their opening can provide a mechanism whereby transmitters, such as glutamate, diffuse out of astrocytes^[56, 69] (Figure 4, mechanism 5). Such release of glutamate through hemichannels occurs under conditions of low extracellular divalent cations, which could occur during pathological conditions with altered divalent cations, like ischemia.

P2X₇ receptors

As alluded to earlier, P2X₇ expression in astrocytes is probably relevant for pathology in the brain, perhaps in ischemia. P2X₇ receptors are ATP-gated pore-forming ion channels that show amplified responses in low external divalent cation solution

(same conditions as for connexon opening) and may provide another pathway for glutamate release from astrocytes^[56, 70] (Figure 4, mechanism 6).

Astrocytes control brain homeostasis

Astrocytes are the main cellular element of extracellular homeostasis in the central nervous system. Numerous transport systems expressed in astroglial membranes provide the control over the concentrations of ions, neurotransmitters, neuromodulators, metabolites and other active molecules in the interstitium.

Ion and water homeostasis

Astroglia has the central role in regulation of extracellular K⁺. Astrocytes remove the excess of extracellular K⁺ via local K⁺ uptake (accomplished by inward rectifier K⁺ channels) and K⁺ spatial buffering^[71, 72]. The spatial K⁺ buffering redistributes K⁺ from the areas with elevated [K⁺]_o to the regions with low [K⁺]_o and may occur either in the single glial cells (K⁺ siphoning in retinal Müller cells^[73]) or within the glial syncytia. In addition astrocytes express aquaporin channels that are primarily responsible for regulation of brain water homeostasis^[74].

Neurotransmitter homeostasis

Astrocytes are responsible for extracellular homeostasis and turnover of various neurotransmitters. In particular astrocytes are central for glutamatergic neurotransmission because they provide for de novo glutamate synthesis, remove glutamate from the extracellular space and sustain the glutamate-glutamine shuttle^[11, 75]. Astrocytes specifically express EAAT1/GLAST and EAAT2/GLT-1 glutamate transporters that accomplish the bulk of glutamate uptake^[76]. Recent experiments in acute slices indicate that ambient extracellular concentration of glutamate might be as low as about 25 nmol/L due to the activity of these transporters^[77]. Glutamate transporters utilise the energy of the transmembrane Na⁺ gradient co-transporting glutamate with Na⁺, H⁺, and K⁺. Activation of glutamate transporter leads to a substantial cytosolic Na⁺ accumulation that is counterbalanced by Na⁺ efflux through Na⁺/Ca²⁺ exchanger working in the reverse mode^[78, 79].

Glutamate, accumulated by astrocytes is enzymatically converted into glutamine by the astrocytic-specific glutamine synthetase; this glutamine then transported to neurones (glutamate-glutamine shuttle) where it provides the source of glutamate for subsequent accumulation into the exocytotic vesicles^[11].

Control of local blood flow and metabolic support

By dividing the grey matter into astroglial territories, astrocytes form neurovascular unit that integrate neural circuitry with local blood flow and metabolic support. The astrocyte couples the brain parenchyma and local vasculature by virtue of perivascular process and the endfeet. Increased neuronal activity triggers Ca²⁺ signals in the astrocyte, which, in turn, stimulate release of vasoactive agents that regulate the local blood flow^[80-82]. Astrocytes also provide local metabolic sup-

port of active neurones through the glucose-lactate shuttle, the activity of which is controlled by increases in cytosolic Na^+ concentration^[83].

Astrocytes in neuropathology

Astrocytes being primary homeostatic cells of the central nervous system are fundamental for the development of all types of neurological diseases. In addition, astrocytes are in a possession of evolutionary conserved defensive programme known as reactive astrogliosis that very much defines the pathophysiological potential of astroglia. Astroglial homeostatic systems exert control over homeostatic imbalances induced by insulting the CNS. The astrogliosis, triggered in response to brain lesions of various aetiology^[84, 85] is essential for limiting the area of damage (by scar formation through anisomorphic astrogliosis) and for the post-insult remodelling and recovery of neural function (by isomorphic astrogliosis). The astroglial homeostatic cascades however can be deleterious, when, upon excessive stress/damage of the nervous tissue, they may aggravate damage to the nervous system. Severe insults may compromise astroglial energetics and ion homeostasis, which in turn can trigger glutamate/ATP release (through reversed transporters or large-conductance plasmalemmal channels), release of K^+ ions that increase neuronal excitotoxicity, release of reactive oxygen species, pro-inflammatory factors and other neurotoxic agents^[86–88].

Astrocytes in acute ischemia

The ischemic infarction that occurs as a consequence of compromised blood flow triggers a specific lesion to the brain parenchyma. In the core of the infarction the cells undergo necrotic death, whereas the surrounding zone of ischemic penumbra still contains viable cells. The spread of the infarction through the penumbra determines the neurological outcome. The survival of cells in the penumbra very much depends on the preserved homeostatic capacity of astroglia. At the same time astroglial syncytia may represent a substrate of death signal propagation; these death signals occurring in the form of spreading waves of astroglial release of glutamate or ATP, developing of brain edema and compromised K^+ buffering^[87, 89].

Astrocytes in epilepsy

Epileptic brain tissue is characterised by profound astroglial reaction with astrocytes undergoing morphological and functional changes^[90]. Focal seizures are associated with astroglial Ca^{2+} signalling^[91] and abnormal glutamate release from astrocytes can be also instrumental in inducing epileptiform seizures. The role of glutamate release from astrocytes in synchronous discharges triggering epileptiform seizures has been proposed^[92]. Finally compromised astroglial glutamate uptake also may contribute to epileptiform activity^[93].

Astrocytes in hepatic encephalopathy (HE)

HE is a potentially-reversible neuropsychiatric abnormality in the setting of both acute and chronic liver failure and it is pri-

marily a disorder of astrocytes^[94]. HE in chronic liver failure is characterized by the presence of “Alzheimer type II” astrocytes, which display morphological abnormalities. Neuronal cell death can be observed in the end-stage of liver failure and it is thought to be associated with the astrocytic dysfunction. The level of expression of several classes of astroglial proteins, including glutamine synthetase and EAATs, has been identified as potential etiological sites for this disorder^[94]. However, discoveries of the presence of vesicular glutamate transporters^[95] and NMDA receptors^[37] in astrocytes, especially when glutamate-mediated bidirectional neurone-astrocyte signalling is considered, may require reinterpretation of the course and treatment of HE.

Astrocytes in other psychiatric disorders

Astroglial cells are also involved in pathological developments in various psychiatric disorders. For example the density of astrocytes was decreased in patients suffering from depression^[96]. Astroglial cells may also be responsible for abnormal glutamate homeostasis which recently is considered as one of the leading pathological mechanisms of schizophrenia^[97].

Astroglia in neurodegenerative diseases

The pathological potential of astroglia in neurodegeneration began to be recognised only very recently. Furthermore it becomes apparent that several types of neurodegenerative diseases are associated astroglial atrophy. Conceptually degeneration of astrocytes may determine early cognitive deficits in neurodegeneration because reduced astroglial support can affect synaptic strength and lead to synaptic loss.

Astrocytes in Alexander disease

Alexander disease is the first discovered example of a primary astroglialopathy^[98]. This disease is a fatal neurodegenerative disease mostly affecting infants and children, causing developmental delay and changes in physical characteristics. Here a defect in astrocytes as a consequence of mutation of the gene encoding for the intermediate filament protein GFAP results in this human disorder. Although the primary target of the GFAP mutations is the astrocyte, the clinical consequences are far more reaching affecting also oligodendrocytes and neurones. At present it is not clear how mutation(s) in GFAP can trigger this devastating disease, but certainly further understanding of the disease mechanisms will aid the development of much needed therapeutics.

Astrocytes in amyotrophic lateral sclerosis (ALS)

Neuroglial reactions play important role in ALS pathology. Prominent astroglial degeneration and atrophy was found in the animal model of Amyotrophic lateral sclerosis (the transgenic mice expressing h(uman)SOD1^{C93A} mutant). The atrophy of astrocytes in this model preceded both neuronal death and the appearance of clinical symptoms^[99, 100]. Reduced support of dopaminergic neurones by astroglial cells may contribute to selective cell death in Parkinson disease^[86]. Astroglial degeneration was also observed in various forms of fronto-tempo-

ral, thalamic and immunodeficiency virus-1 (HIV-1) associated dementia^[101-103].

Astroglia in Alzheimer's disease

Alzheimer's disease (AD) is one of the most feared among other neurodegenerative diseases because of stealth onset, relatively rapid and malignant progression which effectively degrades the human being to a position of a brainless beast. It is generally accepted that AD progression is associated with the parenchymal deposition of beta amyloid (A β) in the form of senile/neuritic plaques, formation of neurofibrillary tangles (NFT), synaptic and neuronal loss. The pathological relevance of neuroglia for AD progression was realised by Alois Alzheimer himself after he discovered the glial cells being an integrative part of senile plaques^[104].

Reactive astrogliosis is the most commonly seen modification of astroglia in the post-mortem human tissues and in the brains of various AD animal models^[105, 106]. Incidentally, the depth of astrogliosis correlates directly with the cognitive decline but not with the β -amyloid load^[107].

Reactive astrogliosis in AD is initiated by many factors, which include signalling from damaged cells as well as extracellular deposition of A β . The exposure of astrocytes to A β also results in an increased gap-junctional coupling in neocortical regions and an increased expression of AMPA/kainate glutamate receptors and glutamate transporters^[108]. The astroglial expression of GLAST- and GLT-1 glutamate transporters was however inhibited in A β -overexpressing transgenic mice^[109].

Recent experiments, however, found another astroglial reaction at the early stages of family AD. In triple-transgenic mice (3xTg-AD; harbouring the mutant genes for amyloid precursor protein (APP_{Swe}), presenilin 1PS1_{M146V} and tau_{P301L}^[109]) a decrease in expression of GFAP and reduced morphological presence of astrocytes was found^[106, 110]. Early atrophic changes in astrocytes may be pathologically relevant as reduced astroglial coverage may lead to synaptic dysfunction and synaptic loss, both processes being prominent at the early phases of the AD. In addition astroglial atrophy may affect a wide range of brain homeostatic processes. Thus astropathology can represent a mechanism for early cognitive decline in AD and probably in other types of senile dementia.

Conclusions

Recent progress in glial neurobiology challenged the neurocentric views on the brain function. The glial cells, which underwent evolutionary explosion in the process of formation of the human brain, assume the most important functions of controlling neural cells development, promoting synaptogenesis, maintaining synaptic transmission and providing for all aspects of nervous system homeostasis. Furthermore, neuroglia represents the brain defence system and failure of glial function results in development many (if not all) of neurological diseases. The glial cells are also involved in various signalling processes, although whether neuroglia is directly responsible for higher brain functions remains the most challenging

question of modern neuroscience.

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