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Astrocytes: The Housekeepers and Guardians of the CNS

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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 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.

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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 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.

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 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, canna-binoid 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). |Geeneration 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).

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 ($[Na^+]_i$) 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.

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 end-foot 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.

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).

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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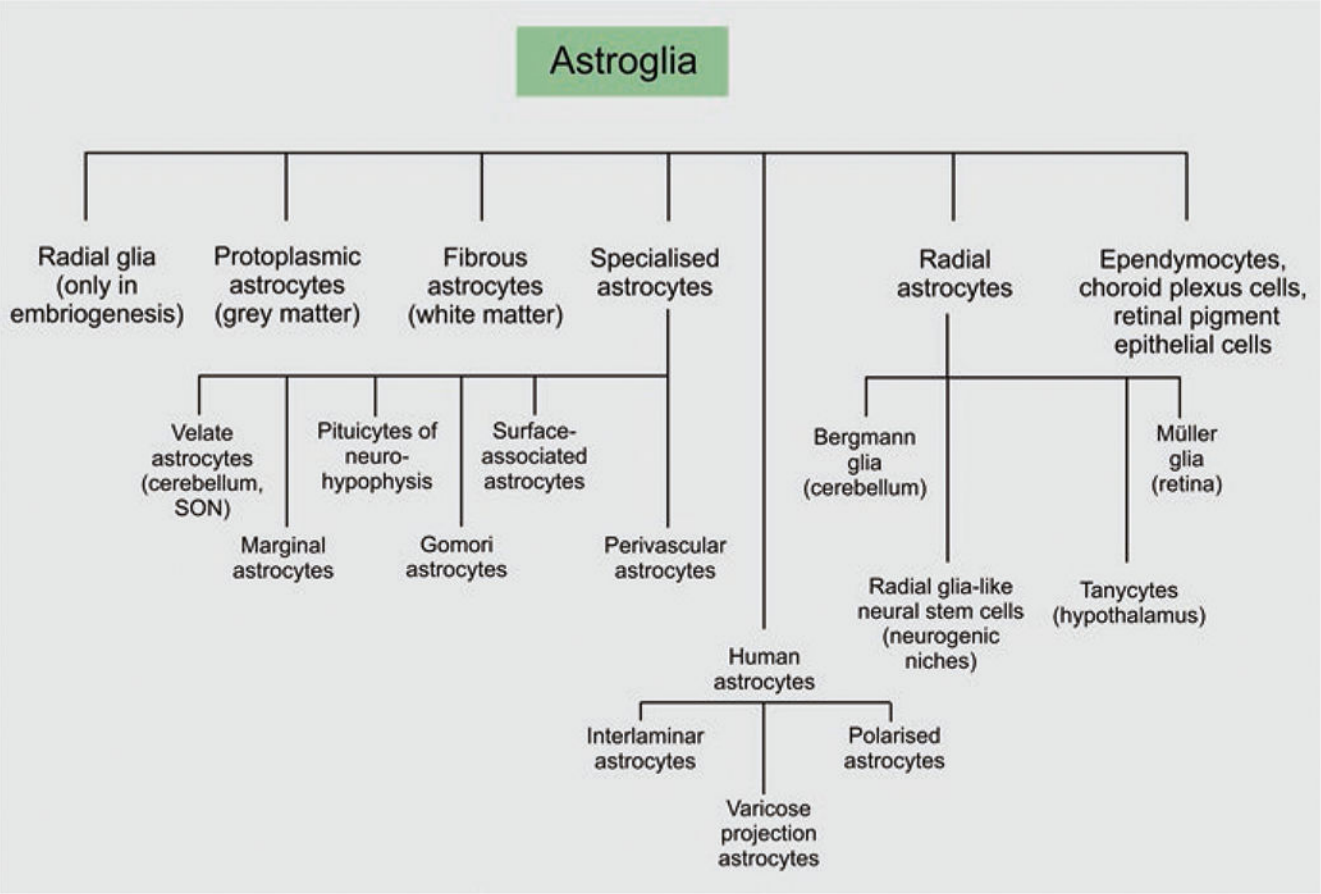

Fig. 1.
Classification of astroglia

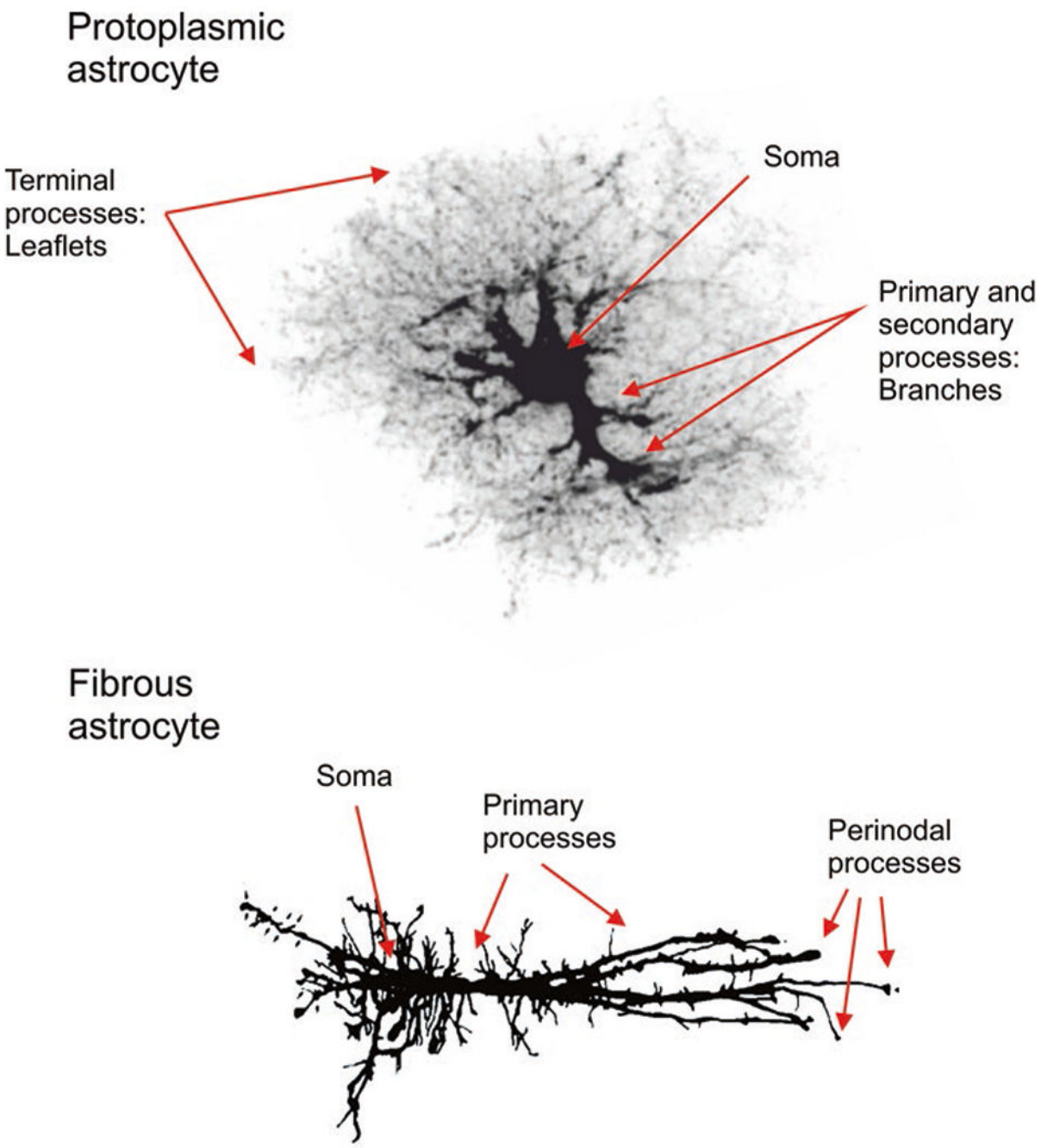

Fig. 2.

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

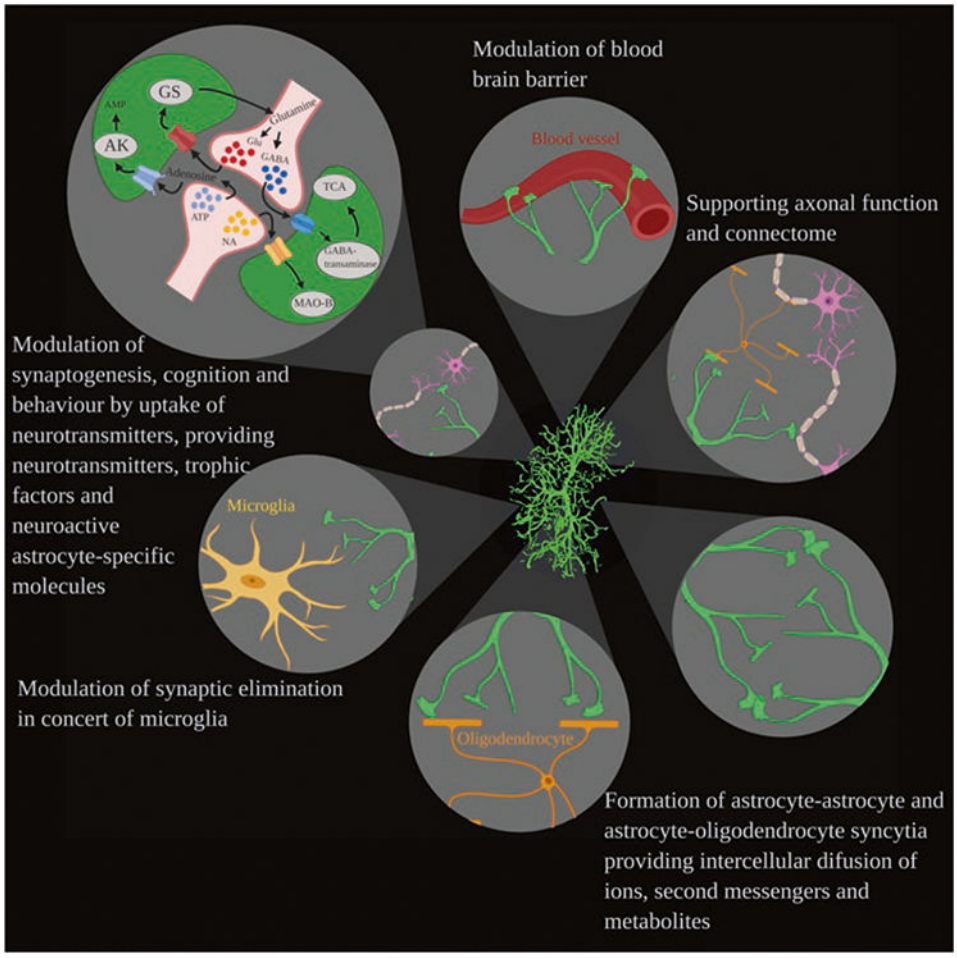

Fig. 3.

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))

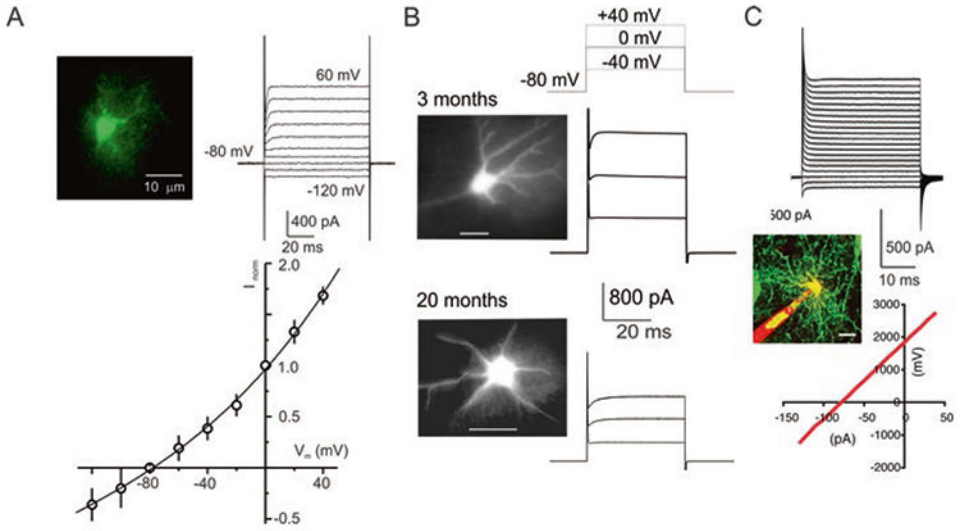

Fig. 4.

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))

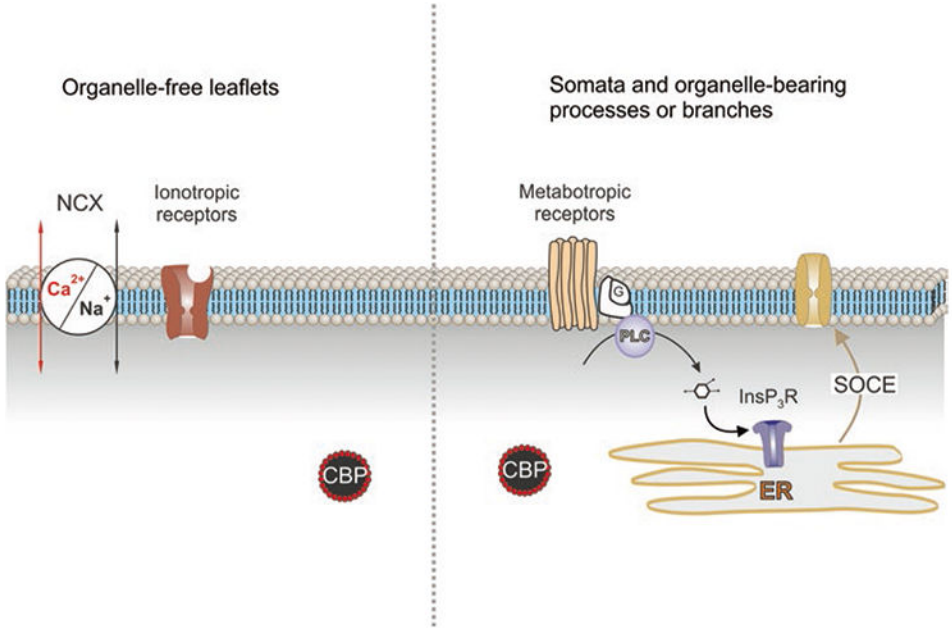

Fig. 5.

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))

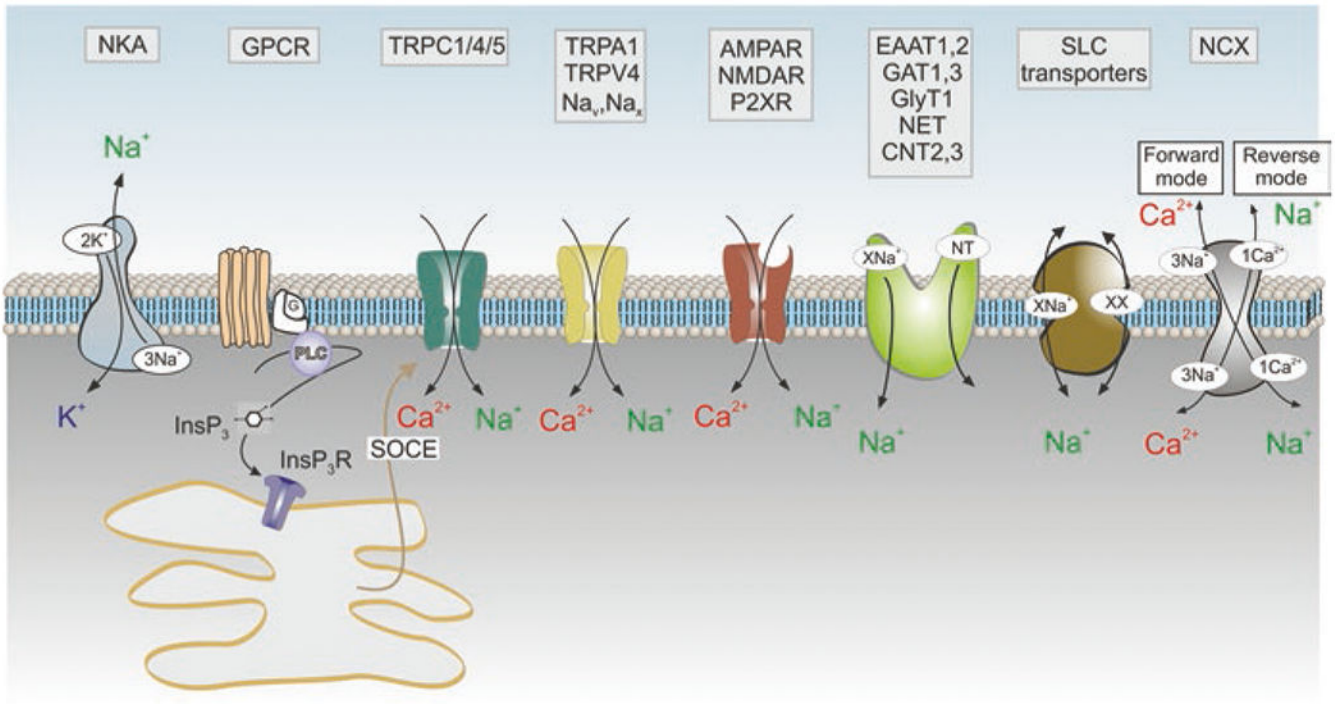

Fig. 6.

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))

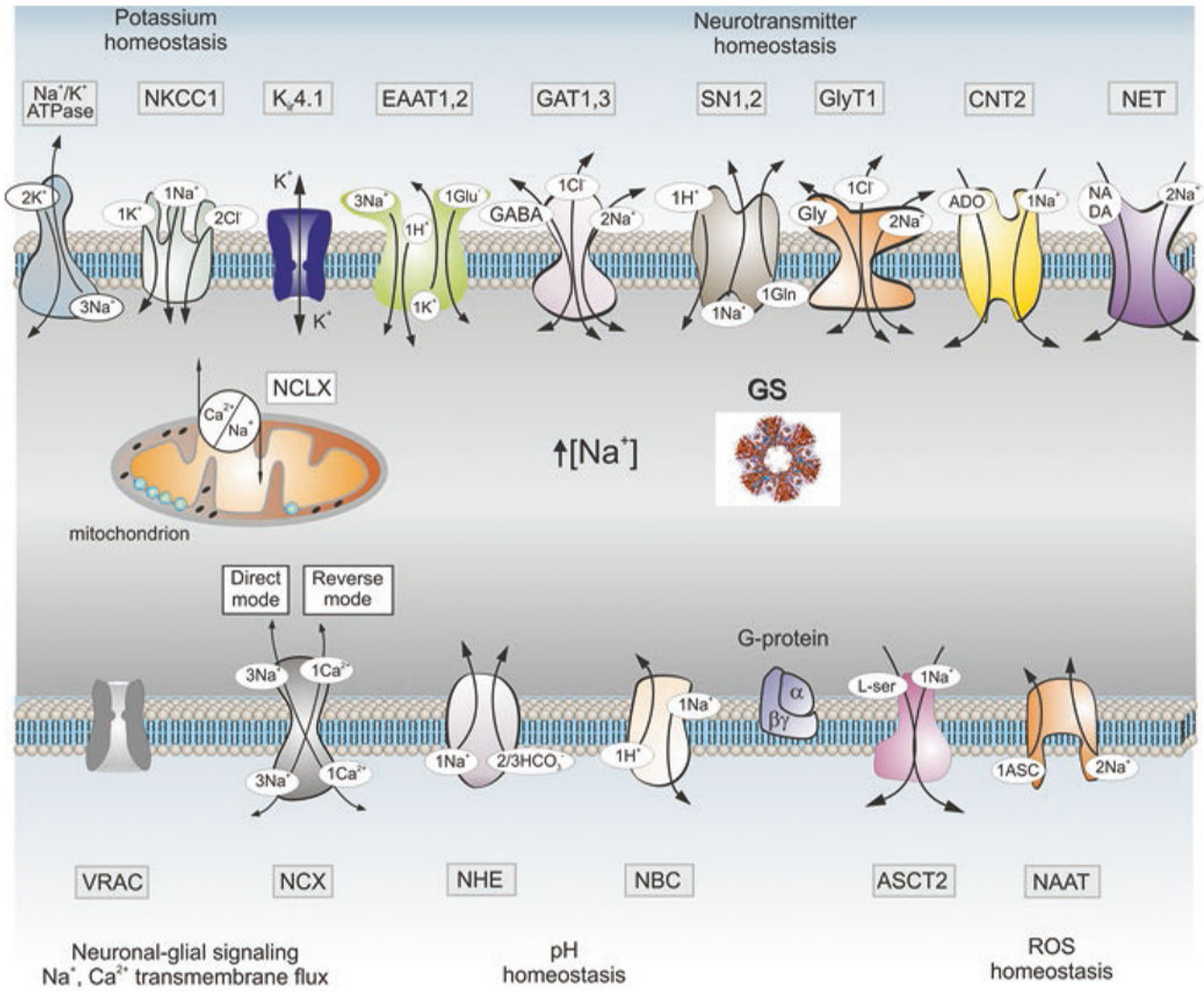

Fig. 7.

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))

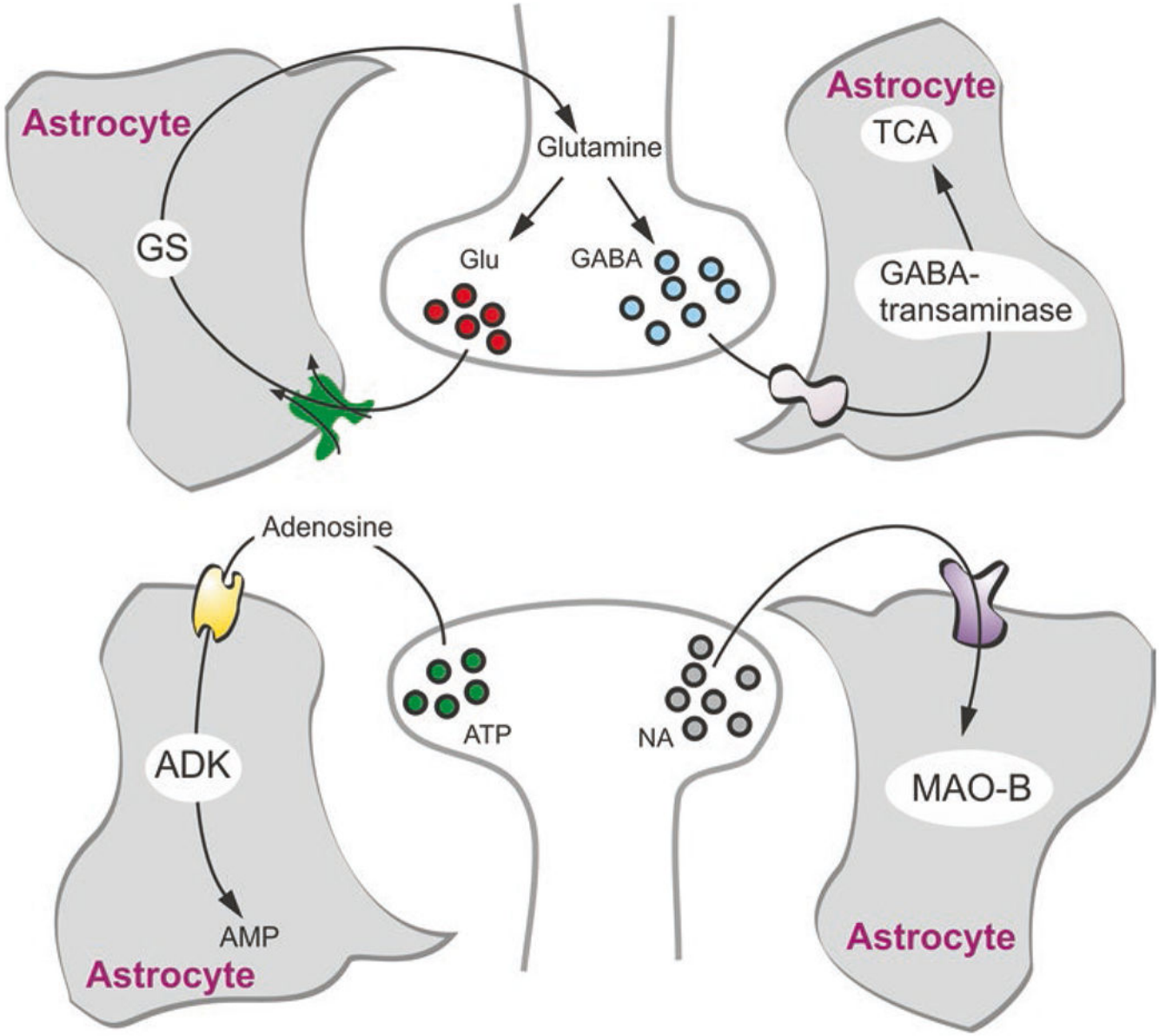

Fig. 8.

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))

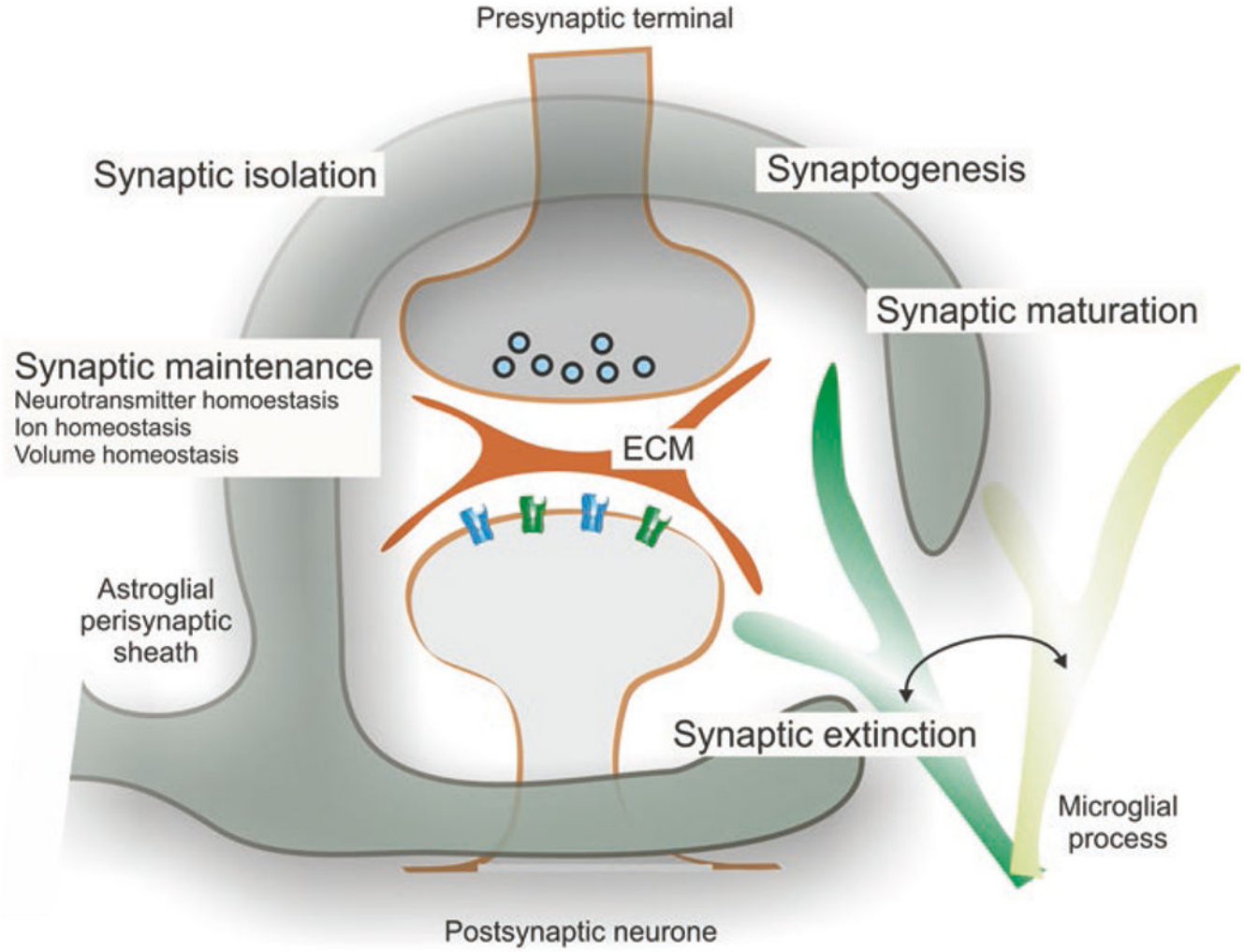

Fig. 9.

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))