Chapter 2
Ionic Signaling in Physiology and Pathophysiology of Astroglia

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Abstract Excitability of astrocytes is based on spatio-temporally organized fluctuations of intracellular concentrations of two ions, Ca^{2+} and Na^{+}. This is dictated by ionic movements between intracellular compartments, and between the cytosol and the extracellular space, achieved by concentration-driven diffusion through membrane channels or transport by pumps and exchangers. Neuronal activity triggers transient elevation of Ca^{2+} and Na^{+} in astrocytes; changes in cytosolic levels of these ions translate into functional responses through multiple molecular cascades. Aberrant ionic signaling contributes to pathological reactions of astroglia in various forms of neurological diseases, such as stroke, epilepsy, and various neurodegenerative and neuropsychiatric disorders.

Keywords Astroglia · Calcium signaling · Sodium signaling · Endoplasmic reticulum · Mitochondria · Ca^{2+} channels · Ionotropic receptors · Metabotropic receptors · TRP channels · Na^{+}- Ca^{2+} exchanger

2.1 Cytoplasmic Ionic Signaling as a Substrate for Glial Excitability

Astrocytes, the "star-like cells", were named by Michael von Lenhossék (Lenhossek 1895) at the end of the nineteenth century. In reality, however, astrocytes rarely have a star-like appearance. Rather, their morphology is extremely heterogeneous

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and if anything, many of them have a spongiform appearance with myriads of very thin distal processes. Incidentally, von Lenhossék was acutely aware of this issue as he wrote: "I would suggest that all supporting cells be named spongiocytes. And the most common form in vertebrates be named spider cells or astrocytes, and use the term neuroglia only *cum grano salis* (with a grain of salt), at least until we have a clearer view." (Lenhossek 1895). At present, the term astroglia is commonly used to define all non-myelinating macroglial cells in the central nervous system (CNS), and these cells are responsible for all conceivable aspects of the brain homeostasis, thus heterogeneous not only in form, but also in function (Verkhratsky et al. 2012; Verkhratsky and Butt 2013). There is no unifying marker that would specifically label all the astroglial cells. Hence, the glial acidic fibrillary protein (GFAP), that is commonly regarded as an astrocytic marker, is not expressed by all the astroglial cells; just to the contrary many of the astrocytes in the mature brain do not express GFAP at identifiable levels. Also, the proportion of astrocytes that express GFAP varies substantially between brain regions, from ~80% in the hippocampus down to only ~10–15% in the neocortex (Kimelberg 2004). Thus, it would be advisable to attain a classification of astrocytes based on multiple markers/antigens as it has been the practice in the field of immunology for a variety of cells. Nonetheless, astroglia, as a class of neural cells, cover classical protoplasmic and fibrous astrocytes, the radial glia, radial Müller retinal glial cells, pseudo-radial cerebellar Bergmann glial cells, laminar and polarized astrocytes of the primate brain, velate astrocytes of the cerebellum, tanycytes that connect ventricular walls with parts of hypothalamus and spinal cord, pituicytes in the neuro-hypophysis, and perivascular and marginal astrocytes (Kimelberg 2010; Kimelberg and Nedergaard 2010; Zhang and Barres 2010; Verkhratsky and Butt 2013). In addition, cells that line the ventricles or the subretinal space represented by ependymocytes, choroid plexus cells and retinal pigment epithelial cells also belong to astroglia.

Homeostatic function of astrocytes is executed on many levels, and once more there is a remarkable heterogeneity in astroglial specialization in various parts of the CNS (Matyash and Kettenmann 2010; Verkhratsky 2010; Zhang and Barres 2010; Verkhratsky et al. 2011). To fulfil such a function, astroglial cells use sophisticated ion signaling systems allowing them to rapidly perceive changes in their immediate neighborhood and rapidly react to them. Although astrocytes are electrically non-excitable, i.e., they cannot generate and propagate action potentials, they possess a form of excitability in which the same ions that mediate electrical signals, by moving charges, act as signaling molecules through binding to multiple effector molecules responsible for astroglial functions. Two main ion signaling systems operative in astroglia are represented by calcium and sodium signaling. These two ions, being transported to and from the cytosol in response to various stimuli, regulate multiple molecular pathways and thus control astroglial function.

2.2 Glial Calcium Signaling

Calcium signaling, which is mediated by dynamic spatio-temporally coordinated changes in free Ca^{2+} concentration in the cellular compartments, has ancient evolutionary roots (Case et al. 2007; Plattner and Verkhratsky 2013) and is universal for most of the life forms on the Earth (Petersen et al. 2005). Changes in free Ca^{2+} concentrations in the cytosol ($[Ca^{2+}]_i$) of astrocytes result from Ca^{2+} fluxes across cellular membranes mediated either by Ca^{2+} diffusion through numerous ion channels down the concentration gradients or by energy-dependent Ca^{2+} transport associated with the activity of Ca^{2+} pumps and exchangers (Kostyuk and Verkhratsky 1995; Verkhratsky et al. 1998; Berridge et al. 2000, 2003; Carafoli 2002; Bregestovski and Spitzer 2005). Importantly, all molecular pathways involved in Ca^{2+} fluxes are regulated by Ca^{2+} ions themselves that constitute a robust feedback control preventing cellular Ca^{2+} overload (Burdakov et al. 2005).

It is generally believed that the chief source of astroglial Ca^{2+} signaling is associated with Ca^{2+} release from the endoplasmic reticulum (ER) Ca^{2+} stores; recent experiments, however, indicated an important role for plasmalemmal Ca^{2+} entry, which, in particular, can assume leading role in shaping Ca^{2+} signals in astroglial perisynaptic processes. Below we shall briefly overview the main pathways for astroglial Ca^{2+} signaling concentrating on the ER, on the plasmalemmal Ca^{2+} entry and on mitochondria.

2.2.1 ER in Astroglial Ca^{2+} Signaling

Astroglial Ca^{2+} signals were discovered and characterized at the beginning of the 1990s (see (Finkbeiner 1993; Verkhratsky and Kettenmann 1996) for overview of early experimental works) in cells in primary cultures (*in vitro*). These experiments identified the astroglial expression of a surprisingly wide array of G-protein coupled receptors, i.e. metabotropic receptors linked to phospholipase C, production of inositol 1,4,5-trisphosphate ($InsP_3$) and subsequent $InsP_3$-induced Ca^{2+} release from the ER (Fig. 2.1). It turned out that almost every neurotransmitter and neuromodulator administered to astrocytes in culture triggers ER Ca^{2+} release. Functional importance of ER in Ca^{2+} signaling in astroglia was subsequently confirmed in experiments *in situ* and *in vivo* (see (Verkhratsky et al. 2012) and references therein), although astrocytes in the brain tissue had much more restricted expression of metabotropic receptor subtypes when compared with *in vitro* conditions. The most common receptors, found in astrocytes in most regions of the brain are represented by metabotropic glutamate receptors of mGluR1 and mGluR5 types, purinoceptors of $P2Y_{1,2,4\,6}$ varieties and α- and β-adrenoreceptors (Kirischuk et al. 1995; Zonta et al. 2003a; Hamilton et al. 2008; Verkhratsky et al. 2009; Hertz et al. 2010; Di Castro et al. 2011), although their patterns can display regional specificity and can change with aging (Sun et al. 2013).

Activation of metabotropic receptors with subsequent $InsP_3$-induced Ca^{2+} release from the ER represents the main mechanism of propagating intra- and intercellular

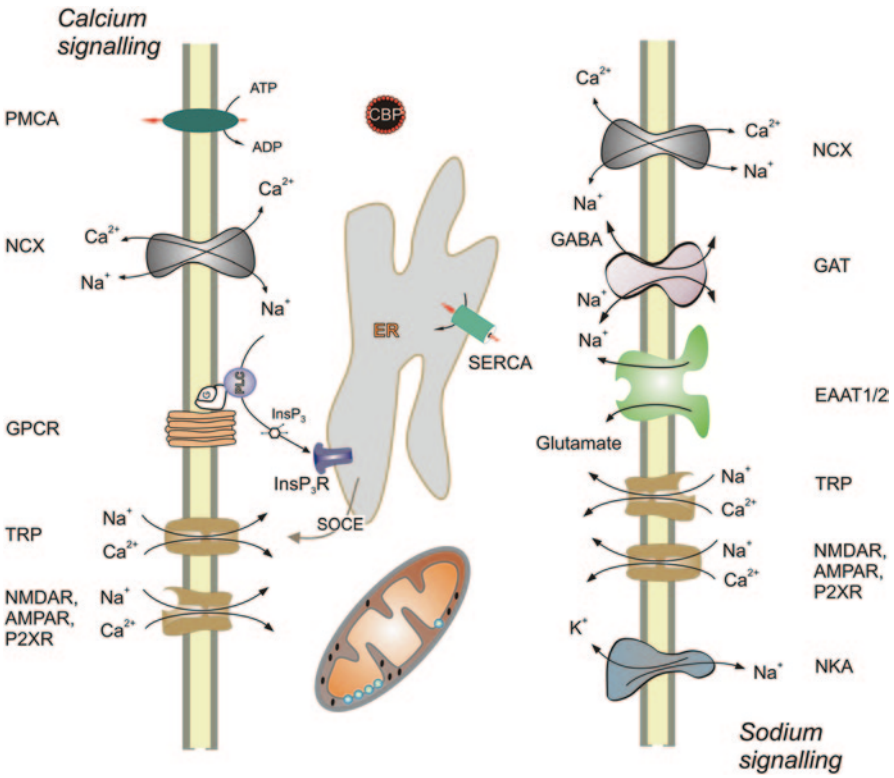

Fig. 2.1 Molecular cascades of calcium and sodium signaling in astroglia. Abbreviations: *AMPAR* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, *CBP* Ca^{2+} binding protein, *EAAT* excitatory amino acid transporter, *ER* endoplasmic reticulum, *GABA* γ-aminobutyric acid, *GAT* GABA transporter, *GPCR* G-protein coupled receptor, *InsP$_3$R* inositol 1,4,5 trisphosphate ($InsP_3$)-gated Ca^{2+} channel/receptor, *NCX* Na^+/Ca^{2+} exchanger, *NKA* Na^+/K^+ ATP-ase, *NMDAR* N-methyl D-aspartate receptor, *PMCA* plasmalemmal Ca^{2+}-ATPase, *P2XR* purinergic 2X receptor, *SERCA* sarco(endoplasmic) reticulum Ca^{2+} ATPase, *SOCE* store-operated Ca^{2+} entry, *TRP* transient receptor potential. (Modified from Parpura and Verkhratsky 2012)

Ca^{2+} waves, the latter commonly considered as a main mechanism for long-range communication in glial syncytia. Propagation of these calcium waves can involve direct diffusion of $InsP_3$ through gap junctions, or astroglial release of neurotransmitters (usually ATP), or combination of both (Giaume and Venance 1998; Scemes and Giaume 2006). At the same time, the role for another ER Ca^{2+} channel, the ryanodine receptor (RyR), in glial calcium signaling remains debatable. Astrocytes express RyRs both at the mRNA and protein level (Matyash et al. 2002; Parpura et al. 2011). Caffeine-induced RyR-mediated Ca^{2+} release was observed in astrocytes in the thalamus (Parri and Crunelli 2003), and inhibition of RyRs was shown to reduce ER stress in astrocytes in culture and in organotypic slices (Alberdi et al. 2013), and yet the physiological role for RyRs in astroglial Ca^{2+} signaling remains questionable (Beck et al. 2004).

What are the consequences and the physiological role of ER Ca^{2+} signaling in astroglia? Several lines of evidence showed that ER Ca^{2+} release is instrumental for initiating exocytotic neurotransmitter release from astrocytes *in vitro* (Reyes and Parpura 2009; Parpura et al. 2011). First, it was demonstrated that the inhibition of Sarco(Endo)plasmic Reticulum Ca^{2+} ATPases (SERCA) by thapsigargin (that causes depletion of the ER from releasable Ca^{2+} due to an unopposed leakage) (Fig. 2.1) almost completely blocked the Ca^{2+}-dependent release of glutamate from astrocytes (Innocenti et al. 2000; Jeremic et al. 2001). Similarly, thapsigargin blocked the mechanically-induced glutamate release from cultured astroglia (Hua et al. 2004). The same effect was observed after treating astrocytes with diphenylboric acid 2-aminoethyl ester that is known to inhibit $InsP_3$ receptors and store-operated Ca^{2+} entry (Hua et al. 2004). Calcium signals originated from the ER initiate the release of vasoactive substances (for example derivatives of arachidonic acid or carbon monoxide) that affect the tone of cerebral arterioles and hence contribute to astroglia-dependent regulation of local blood flow (Zonta et al. 2003b; Mulligan and MacVicar 2004). There are data that Ca^{2+} release from the ER regulates astroglial apoptosis through transactivation of pro-apoptotic factor Bax (Morales et al. 2011). Dynamic changes in ER Ca^{2+} that accompany Ca^{2+} release are also involved in the regulation of multiple ER functions, most notably in controlling the activity of chaperones and protein folding; long-lasting decrease in ER Ca^{2+} level can bring upon ER stress, which contribute to various pathologies (Alberdi et al. 2013). Finally, global astroglial Ca^{2+} signals associated with ER Ca^{2+} release dynamically affect mitochondrial metabolism thus regulating ATP synthesis and providing for activity-metabolic coupling.

At the same time, the role of ER Ca^{2+} release in astroglial physiology *in situ* remains debatable. For example, experiments on genetically modified mice in which ER Ca^{2+} release in astrocytes was specifically affected showed that neither amplification nor occlusion of astroglial metabotropic Ca^{2+} signaling affects synaptic transmission/plasticity in hippocampus (Fiacco et al. 2007; Petravicz et al. 2008; Agulhon et al. 2010). Similarly, ultrastructural study has shown that perisynaptic astroglial processes in hippocampus do not contain ER structures, which are localized mainly in the more proximal processes (Partushev et al. 2013).

These observations revived interest to plasmalemmal Ca^{2+} fluxes that, in particular, can underlie rapid and highly localized Ca^{2+} signals in perisynaptic astroglial processes; these Ca^{2+} signals are critical for the homeostatic control of synaptic cleft and for the regulation of synaptic plasticity.

2.2.2 Plasmalemmal Ca^{2+} Entry in Astrocytes

Astrocytes have several molecular pathways responsible for the generation of transmembrane Ca^{2+} fluxes, which include ionotropic receptors, transient receptor potential (TRP) channels, sodium-calcium exchangers (NCX), and possibly voltage-gated Ca^{2+} channels (Fig. 2.1). The plasma membrane Ca^{2+}-ATPase (PMCA) is the

major Ca^{2+} extruder in resting astrocytes, but it plays a less important role during times of Ca^{2+}cytosolic loads caused by mechanical stimulation (Reyes et al. 2012).

Ionotropic Receptors Astrocytes, both *in vitro* and *in situ*, are endowed with several types of Ca^{2+} permeable ligand-gated channels. The first class of these channels is represented by ionotropic glutamate receptors of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) types; functional expression of kainate receptors in astrocytes has not yet been reported (Parpura and Verkhratsky 2013). The Ca^{2+} permeable AMPA receptors (that lack GluA2 subunit) have been routinely found in cultured astrocytes and their expression is confirmed in Bergmann glial cells in the cerebellum (Steinhauser and Gallo 1996). However, the extent to which Ca^{2+} permeable receptors are present in other brain regions needs further characterization. Nonetheless, Ca^{2+} permeability of GluA2-devoid AMPA receptors is relatively low ($P_{Ca}/P_{monovalent} \sim 1$, (Burnashev et al. 1992)) which, together with rapid desensitization of AMPA receptors in physiological context, very much limits Ca^{2+} entry. In contrast, NMDA receptors, that have been found in mouse cortical astrocytes and also identified in human astroglia (Lalo et al. 2006; Verkhratsky and Kirchhoff 2007; Lee et al. 2010; Lalo et al. 2011), are characterized by much larger Ca^{2+} permeability ($P_{Ca}/P_{monovalent} \sim 3$) and slow desensitization that allows Ca^{2+} influx, resulting in substantial $[Ca^{2+}]_i$ rise in astrocytes studied in acute isolation and in acute brain slices (Palygin et al. 2010). In addition, astroglial NMDA receptors have a weak Mg^{2+} block at physiological resting potential that permits receptor activation by glutamate release during on-going synaptic activity (Lalo et al. 2011). Astroglial Ca^{2+} signaling is also mediated by ionotropic P2X purinoceptors; specific heteromeric P2X receptors are operative in neocortical astroglia (Lalo et al. 2008). These receptors have very high sensitivity to ATP ($EC_{50} \sim 50$ nM) and do not desensitize in the presence of an agonist. They are Ca^{2+} permeable ($P_{Ca}/P_{monovalent} \sim 2$) and, similar to NMDA receptors, mediate $[Ca^{2+}]_i$ signals in astrocytes in isolation and *in situ* (Palygin et al. 2010). Astrocytes in the neocortex were also reported to express $P2X_7$ receptors which, when activated, may provide large Ca^{2+} influx (Norenberg et al. 2010; Oliveira et al. 2011), although these receptors, most likely, mediate pathological responses associated with massive release of ATP (Franke et al. 2012; Illes et al. 2012). Besides ionotropic glutamate receptors and purinoceptors mediated Ca^{2+} entry into astrocytes, these ions can enter through α7 Ca^{2+} permeable nicotinic cholinoreceptors, identified in cultured astroglia (Sharma and Vijayaraghavan 2001; Oikawa et al. 2005).

TRP Channels Astroglia express TRPA1, TRPV4, and TRPC1, 4 and 5 channels, of which TRPC channels are directly involved in Ca^{2+} signaling, being a substrate for store-operated Ca^{2+} entry (Verkhratsky and Parpura 2013; Verkhratsky et al. 2014).

Similarly, Orai channels and their respective currents have been recently recorded in primary cultured astrocytes and astroglial cell lines, which also expressed stromal interacting molecule1 (STIM1), the molecular sensor that monitors the intra-ER Ca^{2+} concentration (Moreno et al. 2012; Motiani et al. 2013).

Astrocytes express TRPC1,4,5 subunits at both mRNA and protein levels (Pizzo et al. 2001; Grimaldi et al. 2003; Golovina 2005; Malarkey et al. 2008). In TRPC

heteromultimers the TRPC1 channel is obligatory subunit, whereas TRPC4 and TRPC5 proteins have an auxiliary role (Strubing et al. 2001; Hofmann et al. 2002). Specific inhibition of TRPC1 channels by either expression down-regulation with an antisense or by exposing cells to a blocking antibody directed at an epitope in the pore forming region of the TRPC1 protein substantially reduced SOCE following metabotropic or mechanical stimulation in cultured astrocytes (Golovina 2005; Malarkey et al. 2008).

Hippocampal astrocytes seem to express TRPA1 mediating "spotty", localized near-membrane, $[Ca^{2+}]_i$ changes (Shigetomi et al. 2012). In cultured astrocytes, these $[Ca^{2+}]_i$ transient were inhibited by the broad spectrum TRP channel antagonist HC 030031 and by anti-TRP silencing RNA, while the TRPA1 agonist allyl isothiocyanate increased frequency of these events. Activity of TRPA1 channels contributed to setting the resting $[Ca^{2+}]_i$ in hippocampal astrocytes (both in culture and *in situ*), as inhibition of these channels resulted in a significant (from ~120 nM to ~50 nM) decrease in basal $[Ca^{2+}]_i$ (Shigetomi et al. 2012).

Sodium/Calcium Exchanger Important molecular pathway regulating Ca^{2+} entry especially in astroglial perisynaptic processes is represented by sodium-calcium exchange mechanism. Astrocytes are in possession of all three types of mammalian Na^+/Ca^{2+} exchangers, the NCX1, NCX2 and NCX3. The NCX molecules are concentrated in the perisynaptic processes and are often co-localized with plasmalemmal glutamate transporters and NMDA receptors (Minelli et al. 2007). The NCX dependent Ca^{2+} transport in astrocytes operates in both forward (Ca^{2+} extrusion) and reverse (Ca^{2+} entry) modes; because of the relatively high cytosolic concentration of Na^+ ions (see below), the reversal potential of NCX is set rather close to astroglial resting membrane potential and therefore even a moderate depolarization or an increase in the intracellular Na^+ readily reverses the NCX and favors Ca^{2+} influx (Kirischuk et al. 2012). The NCX-mediated Ca^{2+} fluxes in both forward and reverse modes are documented for primary cultured astrocytes and astroglial cells *in situ* (Goldman et al. 1994; Kirischuk et al. 1997). Influx of Ca^{2+} through NCX can be activated by cytosolic Na^+ increase following the activation of ionotropic receptors (Kirischuk et al. 1997) or glutamate transporters (Kirischuk et al. 2007); in cultured astrocytes the reverse mode of NCX can be induced by a moderate depolarization (Paluzzi et al. 2007).

Voltage-gated Ca^{2+} Channels (VGCCs) Although there are numerous reports indicating the expression of VGCCs in astrocytes *in vitro* (see (Parpura et al. 2011; Verkhratsky et al. 2012) for details and references), the role for these channels in physiologically relevant Ca^{2+} signaling in astroglia in the brain tissue remains questionable. There are some indications for VGCC-dependent Ca^{2+} dynamics in astrocytes from the neurogenic subventricular zone (Young et al. 2010) and the ventrobasal thalamus (Parri et al. 2001; Parri and Crunelli 2003) and yet these reports remain sporadic and unconfirmed. It might be argued that VGCCs may become important for Ca^{2+} signals in reactively remodeled astroglia. In particular, reactive astrocytes in the hippocampi of young mice, which experienced pilocarpine-induced status epilepticus, showed an increased expression of L- and P/Q- type channels at 1 week and 2 months following an insult (Xu et al. 2007).

2.2.3 Mitochondria in Astroglial Ca^{2+} Signaling

Mitochondria are able to accumulate Ca^{2+} ions from the cytosol through Ca^{2+} ion channels localized in the outer and in the inner membrane; these channels are represented, respectively, by the voltage-dependent anion channels with considerable Ca^{2+} permeability and by the highly selective Ca^{2+} uniporter (composed of the channel protein of mitochondrial calcium uniporter, and auxiliary EF-hand-containing protein that regulates the uniporter, MICU1/CBARA1 (De Stefani et al. 2011)). Mitochondrial Ca^{2+} sequestration has been well documented in astrocytes (Reyes and Parpura 2008). In addition, mitochondria may release Ca^{2+} via mitochondrial Na^+/Ca^{2+} exchanger NCLX (Parnis et al. 2013) and through the mitochondrial permeability transition pore (Basso et al. 2005; Reyes and Parpura 2008).

2.3 Glial Sodium Signaling

2.3.1 Molecular Physiology of Na^+ Signaling

Many astroglial functions are regulated by the transmembrane gradient for Na^+ ions (Verkhratsky et al. 2013c), which in turn is subject to dynamic variations induced by the physiological stimulation of astrocytes. Astroglial sodium homeostasis is somewhat different from that of neurons at least in one parameter: the resting cytosolic Na^+ concentration ($[Na^+]_i$) in astrocytes is about two times higher (Rose and Ransom 1996; Reyes et al. 2012; Unichenko et al. 2012). High levels of $[Na^+]_i$ are important because they set reversal potentials for numerous Na^+-dependent solute transporters expressed in astroglial membrane (Parpura and Verkhratsky 2012). Physiological stimulation of astrocytes *in vitro* or *in situ* by exogenous neurotransmitters, by synaptic inputs, or by mechanical indentation trigger transient elevation of $[Na^+]_i$ by up to 20–25 mM from the resting level. Furthermore, these $[Na^+]_i$ increases may propagate through astroglial syncytia using gap junctions, thus, generating propagating Na^+ waves. These observations led to a concept of astroglial Na^+ signaling (see (Kirischuk et al. 2012; Langer et al. 2012; Parpura and Verkhratsky 2012; Rose and Karus 2013; Verkhratsky et al. 2013c) and references therein).

Increases in $[Na^+]_i$ are mediated through several molecular pathways (Fig. 2.1). Sodium fluxes are generated by all ionotropic receptors present in astroglial membranes, these receptors being, in essence, cationic channels provide for a large Na^+ entry upon their activation (Kirischuk et al. 1997; Langer and Rose 2009). Another important route is associated with the activation of TRPC channels (Reyes et al. 2013), which (through store-operated mechanism) provide a link between ER Ca^{2+} release and plasmalemmal Na^+ flux (Verkhratsky et al. 2014). In astrocytes from subfornical organ Na^+ influx is mediated by Na_x channels sensitive to extracellular Na^+ concentration. Opening of these channels with subsequent Na^+ entry is instrumental for astroglial chemosensing and systemic regulation of Na^+ homeostasis (Shimizu et al. 2007).

Another physiologically important Na^+ influx pathway is associated with the activation of plasmalemmal neurotransmitter transporters for glutamate and GABA, the astroglial specific excitatory amino acid transporters 1 and 2 (EAAT1 and EAAT2) and the GABA transporters of GAT1 and GAT3 types. The stoichiometry of EAAT1/2 is 1 Glu^-:3 Na^+:1K^+:1H^+, of which Na^+, proton and glutamate enter the cell in exchange for K^+ efflux, whereas GAT1 and GAT3 exchange 1 GABA molecule for 2 Na^+ ions and 1 Cl^- anion. Accordingly, in physiological conditions, astroglial uptake of neurotransmitters is accompanied with net Na^+ influx that underlie electrogenicity of transporters and can increase $[Na^+]_i$ by ~20 mM following the activation of EAAT1/2 or by ~7 mM following the activation of GAT1/3 (Kirischuk et al. 2007; Unichenko et al. 2012).

Astrocytes possess Na^+/K^+-ATPase (NKA), a pump which is the major Na^+ extruder in resting astrocytes. However, NKA seems to be less important during times of Na^+ cytosolic loads caused by mechanical stimulation. Instead, NCX operating in reverse mode appeared as a major contributor to the overall Na^+ homeostasis in astrocytes, both at rest and when these glial cells were mechanically stimulated (Reyes et al. 2012).

2.3.2 *Functional Role of Na^+ Signaling*

Increases in $[Na^+]_i$ regulate multiple molecular cascades responsible for astroglial homeostatic function (Fig. 2.2). Elevation in $[Na^+]_i$ activates astroglial NKA, which (i) affects K^+ buffering (Wang et al. 2012) and (ii) triggers lactate synthesis and therefore mobilize astrocyte-neuron lactate shuttle (Pellerin and Magistretti 2012); lactate can be released (or taken up) from astrocytes through the proton-coupled transporter MCT-1. In this way astroglial metabolic support is tailored to the neuronal activity and hence local neuronal energy demands. Changes in $[Na^+]_i$ also directly affect $K_{ir}4.1$ channels that are critical for astroglial K^+ buffering (Kucheryavykh et al. 2012), and regulate other K^+ transporters such as, for example, $Na^+/K^+/Cl^-$ co-transporter NKCC1, which also contributes to K^+ buffering (Kirischuk et al. 2012).

Changes in $[Na^+]_i$ have profound effects on many astroglial solute carriers that are controlling molecular homeostasis of the CNS environment. First and foremost, $[Na^+]_i$ regulates neurotransmitter homeostasis. Both glutamate and GABA plasmalemmal transporters are directly affected by $[Na^+]_i$, albeit with different functional consequences. Physiological increases in $[Na^+]_i$ may slow down, but never reverse glutamate transporters, which have reversal potential ~+60 mV (Kirischuk et al. 2007, 2012). Reversal of glutamate transporter, that has been observed in experiments (Szatkowski et al. 1990), may only occur in pathology when massive $[Na^+]_i$ increase coincides with an increase in cytosolic glutamate concentration and membrane depolarization. In contrast, reversal potential of astroglial GABA transport (~−80 mV) is quite close to the resting membrane potential, and therefore even minute increases in $[Na^+]_i$ (~7 mM) can switch GABA transport into the reverse mode and, thus, mediate GABA release from astroglia (Unichenko et al. 2012).

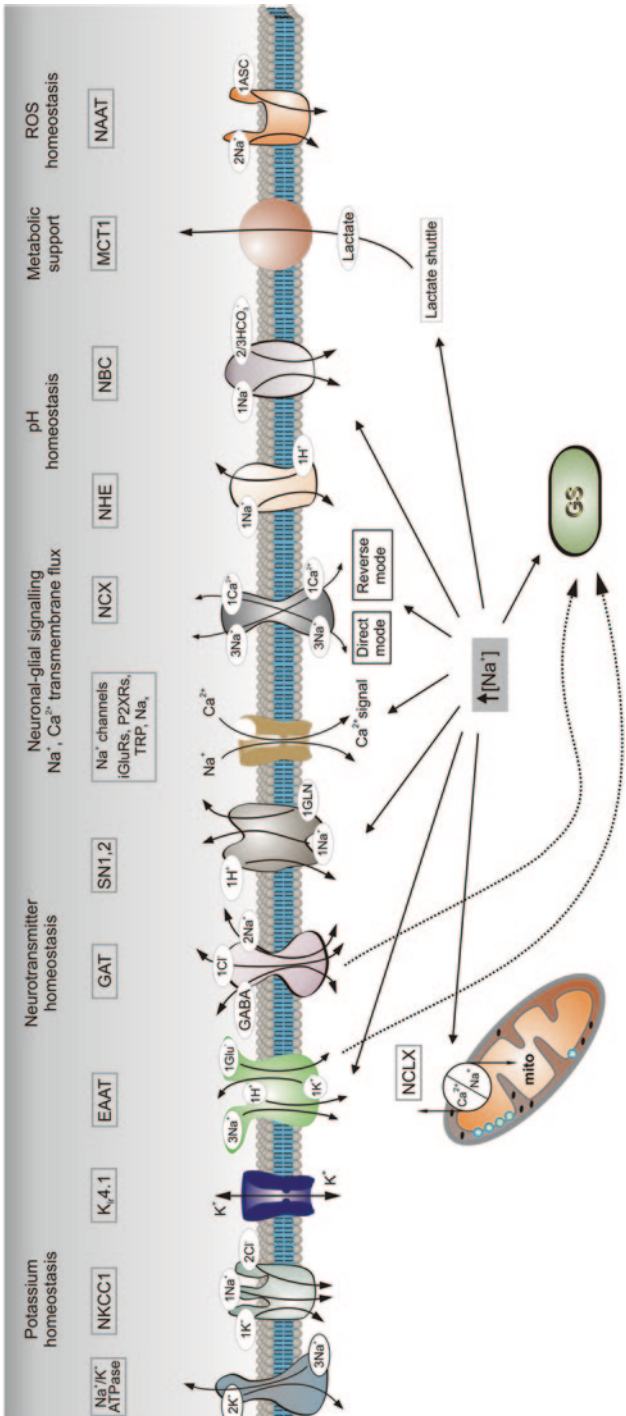

Fig. 2.2 Functional targets of Na^+ signaling in astroglia. Schematic diagram showing receptors and transporters involved in and sensitive to changes in $[Na^+]_i$ and their relations to main homeostatic functions of astroglia. Abbreviations: *EAAT* excitatory amino acid transporters, *GAT* GABA transporters, *GS* glutamine synthetase, *iGluRs* ionotropic glutamate receptors, *mito* mitochondrion, *Kir4.1* inwardly rectifying K^+ channels involved in K^+ buffering, *MCT1* monocarboxylate transporter 1, Na_x Na^+ channels activated by extracellular Na^+, *NAAT* Na^+-dependent ascorbic acid transporter, *NBC* Na^+/HCO_3^- (sodium-bicarbonate) cotransporter monocarboxylate, *NCX* Na^+/Ca^{2+} exchanger, *NCLX* mitochondrial Na^+/Ca^{2+} exchanger, *NHE* Na^+/H^+ exchanger, *NKCC1* $Na^+/K^+/Cl^-$ cotransporter, *P2XRs* ionotropic purinoceptors, *SN1,2* sodium-coupled neutral amino acid transporters 1 and 2 which underlie the extrusion of glutamine, *TRP* transient receptor potential channels. (Modified and updated from Kirischuk et al. 2012)

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