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Physiology of Astroglia

Alexei Verkhratsky,
Faculty of Biology, Medicine and Health, The University of Manchester, Manchester M13 9PT, UK

Faculty of Health and Medical Sciences, Center for Basic and Translational Neuroscience, University of Copenhagen, 2200 Copenhagen, Denmark

Achucarro Center for Neuroscience, IKERBASQUE, Basque Foundation for Science, 48011 Bilbao, Spain

Vladimir Parpura
Department of Neurobiology, The University of Alabama at Birmingham, Birmingham, AL, USA

Nina Vardjan, **Robert Zorec**
Laboratory of Neuroendocrinology-Molecular Cell Physiology, Faculty of Medicine, Institute of Pathophysiology, University of Ljubljana, Ljubljana, Slovenia

Celica Biomedical, Ljubljana, Slovenia

Abstract

Astrocytes are principal cells responsible for maintaining the brain homeostasis. Additionally, these glial cells are also involved in homocellular (astrocyte-astrocyte) and heterocellular (astrocyte-other cell types) signalling and metabolism. These astroglial functions require an expression of the assortment of molecules, be that transporters or pumps, to maintain ion concentration gradients across the plasmalemma and the membrane of the endoplasmic reticulum. Astrocytes sense and balance their neurochemical environment via variety of transmitter receptors and transporters. As they are electrically non-excitable, astrocytes display intracellular calcium and sodium fluctuations, which are not only used for operative signalling but can also affect metabolism. In this chapter we discuss the molecules that achieve ionic gradients and underlie astrocyte signalling.

Keywords

Astrocytes; Brain homoeostasis; Neurotransmitter receptors; Ion channels; SLC transporters; Ca^{2+} signaling; Na^{+} signalling

3.1 Definition of Astroglia

Astroglia (also known as astrocytes) are a class of neural cells of ectodermal, neuroepithelial origin that sustain homeostasis and provide for defence of the central nervous system (CNS) (Fig. 3.1; [410]). The term astrocyte (αστρον κψτοσ; *astron*, *star and kytos*, *a hollow*

A. Verkhratsky Alexej.Verkhratsky@manchester.ac.uk.

vessel, later *cell*; that is a star-like cell) was introduced by Michael von Lenhossék in 1895 [213]; of note, he proposed to name all parenchymal glia spongiocytes, with only a subtype of these cells having characteristic morphology in Golgi's stained preparations being identified as astrocyte. On this matter Lenhossék 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'. The terms of protoplasmic (white matter) and fibrous (grey matter) glia were introduced by Albert von Kölliker and William Lloyd Andriezen [13, 195]).

Astrocytes demonstrate quite heterogeneous morphology across different brain structures (see Chap. 1). Nevertheless, the main physiological features of astroglial cells are somewhat similar, being specifically tailored for their homeostatic function. Astrocytes maintain homeostasis of the CNS at all levels of organisation [408–410] from molecular (ion and transmitter homeostasis, regulation of pH, metabolic energy support, Fig. 3.1), cellular (neurogenesis), network (synaptogenesis and synaptic maturation, maintenance and extinction), organ (regulation of the blood-brain barrier, operation of the glymphatic system) and systemic (chemosensing of oxygen, CO_2 and systemic Na^+ concentration).

In the CNS, astrocytes are integrated into cellular networks (known as syncytia), by gap junctions, which are specialised areas of apposing membranes of adjacent cells pierced by many hundreds of intercellular channels or connexons that form the conduit for intercellular transport of ions, second messengers and other biologically active molecules with a molecular weight lesser than 1000 Da. In the mammalian CNS, astroglial syncytia are anatomically segregated within different anatomical structures. In the sensory cortex, astroglial syncytia are confined to individual barrels and in the olfactory bulb to individual glomeruli [118, 148, 332]. Panglial syncytia that connect astrocytes and oligodendrocytes have been identified in the thalamus, neocortex and hippocampus [59, 123, 181, 296]. Whether astroglia form syncytia with neurones, remains an open issue.

3.2 Membrane Physiology and Ion Distribution

Astrocytes are electrically non-excitable cells, with a rather negative resting membrane potential (V_m) of about −80 mV. Disparity between cytosolic and extracellular ion concentrations (Fig. 3.2), together with the specific membrane ion permeability, define this negative V_m of astrocytes. At rest intra-astrocytic concentration of K^+ is between 120 and 140 mM and extracellular K^+ concentration is about 3 mM, which sets the equilibrium potential for K^+ (E_K) at −98 mV (at 37 °C). Concentration of cytosolic Na^+ in astrocytes (15–20 mM) is generally higher than in the majority of neurones (8–10 mM). With Na^+ concentration in the cerebrospinal fluid (CSF) around 145–155 mM, the corresponding E_{Na} ranges between +55 and +60 mV [192, 331]. Concentration of ionised Ca^{2+} in the cytosol of astrocytes ranges between 50 and 150 nM, which for extracellular $[Ca^{2+}]$ of 1.4 mM sets the $E_{Ca}{}^{2+}$ at +120 to + 140 mV. Cytosolic concentration of free Mg^{2+} in cultured astrocytes measured with a fluorescent probe Mag-Fura-2 is around 125 μM [20]; the CSF Mg^{2+} has been determined at ~0.9 mM [384] giving $E_{Mg}{}^{2+}$ ~ +25 mV.

High cytosolic Cl^- concentration (30–50 mM) has been measured in cultured astrocytes and Bergmann glial cells in cerebellar slices [403]; this sets the E_{Cl}^- around −35 mV (the $[Cl^-]_o$ is ~120 mM). The concentration of protons in astroglial cytosol is ~63 nM (pH 7.2), which, assuming the extracellular H^+ concentration to be ~40 nM (pH 7.4) sets the E_H^+ at ~−12 mV. The cytosol of astrocytes is rich in CO_2 (~1.2 mM) and HCO_3^- (~17 mM).

The most characteristic electrophysiological signature of mature astrocytes is hyperpolarised resting potential (~−80 mV) and low input resistance (5–20 MΩ) indicative of high resting membrane permeability for K^+ [242, 243]; the current to voltage relationship of astroglial cells is nearly linear [2, 73, 161, 168]. Fluctuations of astroglial V_m generally reflect changes in extracellular K^+ concentration [11, 81].

3.3 Ion Channels

3.3.1 Potassium Channels

Glial membrane permeability is dominated by K^+ channels, several types of which are expressed in astrocytes (Fig. 3.3). These channels have distinct voltage-dependence, which covers the whole range of physiological membrane potentials, thus ensuring the passive properties of astroglial plasma membrane. This prominent K^+ conductance of astrocytic plasmalemma defines the homeostatic capabilities of astrocytes [269], supporting movement of ions and providing electrical driving force for membrane transporters.

3.3.1.1 Inward Rectifier Potassium Channels, K_{ir}—Inward rectifying K^+ channels are so-called because they pass K^+ ions more easily into the cell (the inward direction) than out of the cell (the outward direction). The inward rectification occurs due to a voltage-dependent intracellular block by Mg^{2+} and polyamines [225]. These two transmembrane domain channels belong to a gene super-family represented by 16 subtypes (*KCNJ1-KCNJ18*), which are further divided into 7 families from K_{ir}1.x to K_{ir}7.x [139].

The main astroglial inward rectifying K^+ channels are represented by the K_{ir}4.1 subtype (product of *KCNJ10 gene*). These channels are detected in many types of astroglia including protoplasmic and fibrous astrocytes, from all brain areas including hippocampus, neocortex, optic nerve, cerebellum, spinal cord and retina [58, 140, 169], with some regional variations; astroglia such as Müller glia and Bergmann glia express them as well. High K_{ir}4.1 immunoreactivity was detected in hippocampal astrocytes, in astroglial cells in the cerebral cortex, in the deep cerebellar nuclei, in Bergmann glia and in Müller cells but not in astrocytes in white matter [309]. In the spinal cord, the expression of K_{ir}4.1 channels is the highest in astrocytes from the ventral horn and the lowest in astrocytes from the apex of the dorsal horn [273]. The K_{ir}4.1 channels are major contributors to the resting membrane potential of astroglial cells: functional inhibition or genetic deletion of K_{ir} currents markedly increases input resistance (up to 20-fold) and depolarises astrocytes (by ~20 mV) [273, 350].

The K_{ir}4.1 may co-assemble with K_{ir}5.1 channels forming heteromers, which were found in parenchymal and radial astrocytes, in the olfactory bulb, neocortex, cerebellum and retina [50, 138, 159, 251]. The K_{ir}4.1/K_{ir}5.1 heteromeric channels are concentrated in perisynaptic and perivascular processes of astrocytes and their processes close to the pia mater [138].

Some astrocytes in the hippocampus and cerebellum (including Bergmann glia) along with retinal Müller glia were found to express $K_{ir}2.1$, $K_{ir}2.2$ and $K_{ir}2.4$ channels [194, 214, 317, 380]. Astrocytes also express ATP-sensitive inward rectifying K^+ channels assembled from $K_{ir}6.x$ subunit and SUR1/2; these channels open upon intracellular ATP depletion [96, 174, 365, 395, 431].

3.3.1.2 Voltage-Independent K^+ Channels—

Another type of K^+ channels, which contributes to the resting membrane permeability of astrocytes is represented by members of the two-pore-domain potassium channels (K_{2P}) family encoded by 15 KCNK genes [100]. Hippocampal astrocytes were found to express functional TREK1/$K_{2P}2.1$(*KCNK2*), TREK2/$K_{2P}10.1$(*KCNK10*) and TWIK1/$K_{2P}1.1$(*KCNK1*) channels [350, 432]. In cultured cortical astrocytes and astrocytes in hippocampal slices expression of TWIK-1/TREK-1 heterodimer (formed by disulphide bridge between cysteine-cysteine residuals of both subunits) has been demonstrated as the predominant channel type [156].

3.3.1.3 Voltage-Gated K^+ Channels, K_V—

Astrocytes express delayed rectifying (K_D) and transient (K_A) voltage-gated K^+ channels. The delayed rectifying K^+ currents were identified in astrocytes throughout the CNS including the cortex, hippocampus, cerebellum and spinal cord [48]. At the molecular level, $K_v1.5$ (*KCNA5*), $K_v1.4$ (*KCNA4*) and $K_v11.1$/ERG1 (KCNH2) have been identified in astrocytes from the hippocampus and spinal cord [97, 98, 334]. Astrocytes are also in possession of fast (rapidly activating and inactivating) A-type K^+ currents mediated by K_v1, K_v3 and K_v4 channels [32].

3.3.1.4 Ca^{2+}-Dependent K^+ Channels, K_{Ca}—

Several types of Ca^{2+}-dependent K^+ channels (K_{Ca}) were found in astrocytes in vitro and in situ. At the mRNA level SK (small conductance K_{Ca} 2.3/KCNN3) and IK (intermediate conductance $K_{Ca}3.1$/KCNN4) channels were detected in mouse cortical astrocytes in acutely isolated slices [222]. The $K_{Ca}2.3$ immunoreactivity was found in astroglial processes in the rat supraoptic nucleus [17]. BK (big conductance) channels ($K_{Ca}1.1$/KCNMA1) were identified in the perivascular astroglial endfeet in the hippocampus and cerebellum [315], whereas patch-clamp recordings obtained from endfeet revealed large-conductance (225 pS) BK-single channel currents [107].

3.3.2 Sodium Channels

3.3.2.1 Voltage-Gated Sodium Channels—

Although being non-excitable cells, astrocytes express voltage-gated Na^+ channels (Na_v), which were detected in vitro and in situ, albeit at low density [26, 28, 42, 371–374]. Cultured astrocytes from the optic nerve, hippocampus and spinal cord were found to express fast tetrodotoxin (TTX)-sensitive and slow TTX-resistant Na^+ currents [373, 374]. At the molecular level astrocytes mainly express $Na_v1.5$ subunit which was identified both in vitro and in situ at mRNA and protein levels [40, 41, 286]; relatively low expression of $Na_v1.2$, $Na_v1.3$ [44] and $Na_v1.6$ [321, 345] were also detected; incidentally expression of $Na_v1.6$ channels was found to increase in reactive astroglia [434].

Distribution of Na^+ channels in astrocytes from different brain regions as well as their physiological role remain poorly understood; hitherto Na^+ currents have not been recorded from astroglial cells in vivo. Possibly voltage-gated Na^+ channels contribute to Na^+ signalling; it was also suggested that Na^+ influx mediated by these channels is needed for sustained activity of Na^+/K^+ pump (see [43, 285, 287] for further details).

3.3.2.2 $[Na^+]_o$-Regulated Na^+ Channels, Na_x—

Specific type of Na^+ channels regulated by extracellular Na^+ concentration ($[Na^+]_o$) are named Na_x channels. They are expressed in astrocytes of the subfornical organ and organum vasculosum of the lamina terminalis (that are parts of circumventricular organs surrounding ventricles, structures where the blood-brain barrier is not as tight as in other parts of the brain) [267, 420]. These channels in vitro are opened following an increase in $[Na^+]_o$ to 150 mM. In vivo, in the presence of endothelin-3, which activates ET_B receptors expressed in astroglia, the threshold for Na_x channel activation is lowered to 140 mM of $[Na^+]_o$ [141]. The Na_x channels appear to operate as molecular sensors for $[Na^+]$ in the circulation (Fig. 3.4).

3.3.2.3 Epithelial Sodium Channel, ENaC—

The epithelial Na^+ channels are non-voltage gated, amiloride-sensitive Na^+ channels widely expressed in the CNS [10, 238, 416]. Immunohistochemistry found strong expression of ENaCs in astrocytes in circumventricular organs, white matter and pia mater [237]. These channels, together with Na_x channels, may be involved in the regulation of systemic Na^+ homeostasis.

3.3.3 Calcium Channels

3.3.3.1 Voltage-Gated Ca^{2+} Channels—

Early patch clamp recordings from astrocytes in culture revealed Ba^{2+} and Ca^{2+} currents sensitive to classic voltage-gated Ca^{2+} channel antagonists and enhanced by norepinephrine or by an increase in cytosolic 3′,5′-cyclic adenosine monophosphate, i.e. cAMP [27, 72, 228], the signalling by this second messenger complementing Ca^{2+} signalling in astrocytes [146]. Subsequently $Ca_v1.2$ and $Ca_v1.3$ channels were detected in the transcriptome of rodent cortical astrocytes [60, 430]. Several types of Ca^{2+} channel subunits (α1B or N-type, α1C/D or L-type, α1E or R-type and α1G or T-type) were detected at mRNA and protein levels in astrocytes in culture [209]. Pituicytes analysed immunohistochemically in situ were found to possess $Ca_v2.2$ (N-type) and $Ca_v2.3$ (R-type) channels [418]. Evidence for functional activity of voltage-gated Ca^{2+} channels in situ is rather thin and indirect (see for example [215, 294]) and no evidence from the in vivo experiments exist at all. There are some indications for increased expression of voltage-gated Ca^{2+} channels in pathological or reactive astrocytes [419, 421].

3.3.3.2 Orai or Ca^{2+}-Release Activated Ca^{2+} Channels—

The Ca^{2+}-release activated Ca^{2+} channels of Orai family (Orai1,2,3) represent one of the main molecular pathways of the store-operated Ca^{2+} entry (SOCE) in non-excitable cells [289]. Activation of these plasmalemmal channels is controlled by the stromal interacting molecules, STIM1 and STIM2, which act as Ca^{2+} sensors of the endoplasmic reticulum (ER) [368]. In cultured astrocytes Orai1 and STIM1 were detected at a protein level; over-expression of Orai1 increased the amplitude of SOCE, whereas siRNA knock out decreased SOCE [248]. Electrophysiological recordings of I_{CRAC} performed on acutely dissociated Müller cells demonstrated sensitivity of the current to ORAI inhibitor Synta 66 [246].

3.3.3.3 Ca^{2+} Release Channels—

Release of Ca^{2+} from the ER store in astrocytes is mainly mediated by Inositol 1,4,5-trisphosphate receptors ($InsP_3R$), of which type 2 predominates [133, 144, 354, 356, 414]. Genetic deletion of $InsP_3R$ type 2 ($InsP_3R2$) has been shown to significantly reduce or even completely abolish Ca^{2+} signalling in astroglial cells from the hippocampus and cortex [171, 302]. Other studies, however, reported $[Ca^{2+}]_i$ transients in $InsP_3R2^{-/-}$ mice astrocytes [130]. There is evidence for functional expression of $InsP_3Rs$ type 1 and 2 in astroglia [125, 327, 357].

Ryanodine receptors also have been identified in astrocytes [364, 414], although their functional role remains unclear. They supply Ca^{2+} necessary for Ca^{2+}-dependent glutamate release from cortical astrocytes in culture. Ca^{2+}-dependent glutamate release involves two classes of ER Ca^{2+} stores in astrocytes [150]. There is some evidence for astroglial expression of the two-pore channels (TPC) that release Ca^{2+}, and are activated by nicotinic acid adenine dinucleotide phosphate, i.e. NAADP [25, 301].

3.3.4 Transient Receptor Potential (TRP) Channels

Astrocytes express several types of cationic channels of TRP (transient receptor potential) family (Fig. 3.5). The ‘ankyrin’ channel TRPA1 was found in somata and processes of astrocytes in the brain stem in the rat trigeminal caudal nucleus using immunogold electron microscopy [211]. Functional expression of TRPA1 was also demonstrated in a sub-population of hippocampal astrocytes [360, 362]. The TRPC (‘canonical’) channels were detected in freshly isolated and in primary cultured astrocytes, which were reported to express all subtypes of these channels from TRPC1 to TRPC6 [124, 244, 308]. These TRPC channels contribute to astroglial Ca^{2+} signalling induced by purinergic, glutamatergic and mechanical stimulation [231, 323, 324]. Astroglial TRPC channels represent a substantial pathway for store-operated Ca^{2+} entry in astroglia [412].

Rodent astrocytes from the brain and the spinal cord have been also reported to express TRPV1 channels [91, 151, 398]. Similarly TRPV4 channels have been identified in cortical and hippocampal astrocytes [22, 33, 57, 220]; these channels can be activated by hypo-osmotic stress and by cell swelling [33, 57] in the absence of addition of membrane by exocytosis [283].

3.3.5 Hyperpolarisation-Activated Cyclic Nucleotide-Gated (HCN) Channels

The cationic (Na^+/K^+) HCN channels are found in both healthy and reactive astrocytes in situ [145, 337].

3.3.6 Acid-Sensitive Ion Channels

The acid-sensitive ion channels (ASIC1–3) were described in reactive astrocytes in the context of chronic epilepsy, and their activation was claimed to contribute to seizure generation [423].

3.3.7 Anion Channels

Astrocytes express the following anion channels: (i) cystic fibrosis transmembrane conductance regulator or CFTR channels, (ii) voltage-dependent anion-selective channels or

VDAC, (iii) Ca^{2+}-dependent Cl^- channels (iv) volume-regulated anion channels or VRAC and (v) ClC-1, −2 and −3 channels [186, 291, 410, 429]. The ClC-2 channels are concentrated in astroglial processes enwrapping GABAergic synapses [363], which may indicate their role for regulation of intra-cleft Cl^- concentration and hence of GABAergic transmission. Astrocytes also express an anion channel of Bestrophin (*Best*) family; these channels were suggested to contribute to the Ca^{2+}-dependent secretion of glutamate and GABA [290, 422].

3.3.8 Aquaporins

Three types of aquaporins, the AQP1, AQP4 and AQP9 were identified in astroglia although AQP4 is the most abundant [21, 256, 342]; the plasma membrane contains mainly the AQP4e isoform [219, 313]. Astroglial AQP4 channels are concentrated in the perivascular and subpial endfeet [256]. Genetic deletion of AQP4 affects olfaction [224] and hearing; it results in a decrease in astroglial water permeability [370], deficient K^+ buffering, compromised volume regulation [39, 219], and deficits in synaptic plasticity [346, 367], and memory [367, 427].

3.3.9 Connexons

Connexons form gap junctional channels that integrate astrocytes into functional syncytia, subject to regulation by G-protein coupled receptors [392]. Astrocyte-astrocyte homocellular gap junctions are composed of Cx26, Cx30 and Cx43 [117, 198, 258], of which Cx43 is the most abundant [257]. The Cx43 is expressed in astroglial cells in all CNS regions, whereas Cx30 is mostly expressed in the thalamus and leptomeninges [257, 369]. The Cx26 subtype has been detected in astrocytes in the hypothalamus, reticular thalamic and subthalamic nuclei [259]. Astrocyte-oligodendrocyte heterocellular gap junctions are composed of heterotypic channels represented, in vitro, by four complexes: Cx47/Cx43, Cx47/Cx30, Cx32/Cx30 or Cx32/Cx26 [230], although in situ Cx32/Cx30 and Cx47/Cx43 complexes appear to predominate [8, 277]. There are some sporadic reports of astrocyte-neuronal heterocellular contacts [9, 255, 279], and these contacts are arguably limited to developing brain.

Unpaired connexons, or hemichannels, have been identified in astrocytes in vitro and in vivo; all three major connexons (Cx26, Cx30 and Cx43) expressed in astrocytes can act as hemichannels [119]. The hemichannels are non-operational in healthy astrocytes, but can be activated by low external calcium concentration, by substantial depolarisation, by some specific intracellular Ca^{2+} signals, or by exposure to pro-inflammatory agents [274, 275]. The hemichannels can contribute to secretion of neurotransmitters and neuromodulators [293] and are subject to regulation via transmitters and G-protein coupled receptors.

3.3.10 Pannexons

Transcripts for pannexin 1 (Panx1) were identified in astroglia in vitro and in situ [153, 320], with Panx1 currents characterised in cultured cortical astrocytes [157]. Astroglial pannexons are activated by voltage and by activation of $P2X_7$ receptors; they are inhibited by broad-spectrum gap junction antagonists carbenoxolone and mefloquine, and they are permeable to fluorescent tracer YoPro [157]. Panx1 containing pannexons have been considered as a transmembrane conduit for ATP [78].

3.4 Receptors

Conceptually, astrocytes have been shown to express virtually any type of receptor found in the CNS. At the same time the pattern of receptors expressed by astrocytes in situ and in vivo is restrictive and is regulated by the local neurochemical environment [183, 410, 411].

3.4.1 Purinoceptors

3.4.1.1 Adenosine Receptors—All four types of adenosine receptors (A_1, A_{2A}, A_{2B} and A_3) were found in astrocytes in the in vitro and in situ preparations [84]. These receptors are linked to intracellular second messenger systems including $InsP_3$, Ca^{2+} and cAMP cascades (Fig. 3.6). Activation of A_1 receptors triggered intracellular Ca^{2+} release as well as Ca^{2+} entry and potentiated histamine-induced Ca^{2+} mobilisation [297, 310]. Similarly, A_{2A} receptors were responsible for Ca^{2+} signalling in astrocytes from the olfactory bulb [90], whereas A_{2B} receptors triggered Ca^{2+} signals in cortical astroglia [306]. The A_3 receptors mediated adenosine- and guanosine-evoked $[Ca^{2+}]_i$ transients in cultured mouse astrocytes [68].

3.4.1.2 P2X Purinoceptors—Transcripts for all seven types of ionotropic purinoceptors ($P2X_1$-$P2X_7$, Fig. 3.6) have been detected in astrocytes in vitro and in tissue extracts [89, 109, 113, 162]. At the protein level, $P2X_{2,3,4}$ receptors were found in astrocytes from the nucleus accumbens [109]. $P2X_1$ and $P2X_2$ receptors were found in astroglial cells in the cerebellum [173, 221]; $P2X_4$ receptors were identified in astrocytes from the brainstem [18] and in Müller glia [142], whereas hippocampal astrocytes were immunoreactive for $P2X_{1–4}$, $P2X_6$ and $P2X_7$ receptors [197].

Ion currents mediated by heteromeric $P2X_{1/5}$ receptors were characterised in cortical mouse astrocytes [204]). These receptors contribute to 'glial synaptic currents' monitored in astrocytes in response to stimulation of neuronal afferents [200, 203]; in addition $P2X_{1/5}$ receptors produced spontaneous 'miniature' post-synaptic currents in astrocytes in cortical slices [203]. Astroglial $P2X_{1/5}$ receptors have intermediate Ca^{2+} permeability ($P_{Ca}{}^{2+}/P_{monovalent} \sim 2.2$), and their activation by endogenous agonosts, or by synaptically released ATP, triggers transient cytoplasmic Ca^{2+} signals [281].

Astrocytes have been reported to express $P2X_7$ receptors both in healthy and pathological contexts [111, 158]. In astrocytes in vitro $P2X_7$ receptors were detected at mRNA and protein levels [89, 93, 113, 154, 164, 260, 282, 417]. Astroglial expression of $P2X_7$ receptors, as a rule, increases after brain injury of various aetiology [109, 110, 260]. In astrocytes in culture both $P2X_7$-mediated Ca^{2+} signals and membrane currents have been detected [93, 113, 266, 268, 335]. Astroglial $P2X_7$ currents were also characterised in rat and mouse cortical slices. Activation of $P2X_7$ receptors in cultured astrocytes may be associated with release of glutamate, GABA, ATP [24, 93, 94, 382]. The $P2X_7$-mediated release of glutamate was also identified in astrocytes in hippocampal slices [106].

3.4.1.3 P2Y Receptors—

Astrocytes in cortex express transcripts for $P2Y_{1,2,4,6,12,13}$ and UDP-glucose $P2Y_{14}$ receptor [1, 36, 89, 113], whereas spinal cord astrocytes predominantly express mRNA for $P2Y_{1,2}$ receptors [104]. Stimulation of astroglial P2Y receptors triggers Ca^{2+} signals originating from $InsP_3$-induced ER Ca^{2+} release [38, 56, 160, 163, 175, 298, 299, 407].

3.4.2 Glutamate Receptors

3.4.2.1 Ionotropic Glutamate Receptors—

Astrocytes from different regions of the brain express α-amino-3-hydroxy-5-methyl-isoxazole propionate (AMPA) receptors (Fig. 3.7), which have been characterised at expression and functional levels. All main subunits of AMPA receptors (GluA1-GluA4) have been detected in astroglial cells. In the hippocampus, AMPA receptors are assembled predominantly from GluA2 and GluA4 subunits, which are reflected by a linear I-V relation and low Ca^{2+} permeability [351]. In cortical astrocytes these receptors are composed of GluA1 and GluA4 subunits [75]. In Bergmann glial cells AMPA receptors do not contain GluA2 subunit, and accordingly they have a double-rectifying I-V relationship and low ($P_{Ca}{}^{2+}/P_{monovalent} \sim 1$) Ca^{2+} permeability [115, 253]. Conditional deletion of AMPA receptors, composed of GluA1 and GluA4 subunits, from Bergmann glia led to a retraction of glial perisynaptic processes and deficient fine motor coordination [338].

Astrocytes also possess functional N-methyl D-aspartate (NMDA) receptors. The transcriptome of human astroglia contains all 7 NMDA receptors subunits (GluN1, GluN2/A-D and GluN3A,B-[210]). In acute slices the NMDA-mediated currents and Ca^{2+} signals were found in astrocytes in the neocortex [202, 272, 348], in the spinal cord [437], and in some cells in the hippocampus [311, 376]. Astroglial NMDA receptors heterotetramers assembled from obligatory two GluN1 and additional subunits of each GluN2 C or D and GluN3; this composition underlies a weak Mg^{2+} block (which develops at ~−120 mV) and relatively low Ca^{2+} permeability ($P_{Ca}/P_{monovalent} \sim 3$), as well as sensitivity to memantine and GluN2C/D subunit-selective antagonist UBP141 [95, 203, 280, 281].

3.4.2.2 Metabotropic Glutamate Receptors—

The most abundant type of astroglial metabotropic receptors in mature CNS is represented by mGluR3, which inhibits adenylyl cyclase [385]. In younger animals astrocytes express mGluR1/5 receptors linked to Ca^{2+} signals and $[Ca^{2+}]_i$ oscillations [76, 191, 208, 312].

3.4.3 GABA Receptors

Astrocytes express both ionotropic $GABA_A$ and metabotropic $GABA_B$ receptors. The $GABA_A$ receptors mediated Cl^- currents have been characterised in astroglial cells in culture and in situ in the hippocampus, cerebellum, retina, hypothalamus, supraoptic nucleus and spinal cord [74, 179, 180, 182, 229, 252]. The subunit composition of astroglial $GABA_A$ receptors is not certain; α1 and β1 subunits were detected in hippocampal astrocytes [112] and α2 and γ1 in Bergmann glia [326]. Metabotropic $GABA_B$ receptors evoke astroglial Ca^{2+} signalling by triggering Ca^{2+} release from the ER [264].

3.4.4 Glycine Receptors

Glycine receptors mediate Cl^- currents in astrocytes in the spinal cord slices [295]. Single-cell RT-PCR performed on these astrocytes revealed expression of α1 and (in ~50% of cells) β-subunits of the receptor [188].

3.5 Acetylcholine Receptors

The ionotropic nicotinic acetylcholine receptors (nAChRs) have been characterised in astrocytes in culture and in acute slices. Activation of these receptors mediates Ca^{2+} influx and triggers Ca^{2+}-induced Ca^{2+} release [271, 353, 389]. Analysis of mRNA expression in rodent cortical astrocytes found α4, α7 and β2 subunits, whereas in human astroglial cells from the hippocampus and entorhinal cortex α3, α7 and β4 subunits were identified by immunocytochemistry [121, 390].

The metabotropic M_1 and M_2 AChRs mediate Ca^{2+} signalling in astrocytes from hippocampal slices [15].

3.6 Receptors for Monoamines

Astroglial cells express receptors for major monoamines including adrenoceptors, and receptors for serotonin, dopamine and histamine. Both α- and β-adrenoceptors have been identified and characterised in astrocytes in culture, in slices, and in vivo at transcript, protein and functional levels [14, 135]. The α_1-adrenoceptors are coupled to phospholipase-C (PLC) and $InsP_3$ signalling and hence to Ca^{2+} release from the ER [55, 193, 352]. Immunoreactivity for α_2-adrenoceptors was found in astrocytic processes in the brain tissue [14, 239]; activation of α_2-adrenoceptor also triggers Ca^{2+} signalling [265, 339]. β_1-, β_2- and β_3-adrenoceptors were characterised in astrocytes in vitro and in vivo [62, 232, 352]. β_1-adrenoceptors contribute to regulation of glycogen synthesis, while β_2-adrenoceptors coupled to adenylyl cyclase through G_s proteins together with possibly β_3-adrenoceptors regulate glucose uptake by modulating GLUT1 plasmalemmal glucose transporter [92, 155].

Astrocytes express 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B} and 5-HT_{5A} metabotropic serotonin receptors, [19, 61, 341]. 5-HT_2 receptors activate PLC/$InsP_3$/Ca^{2+} signalling cascade [341]. 5-HT_{2B} receptor seems rather abundant in astrocytes [196] with its expression as twice as large as in neurones [428]. Serotonin-specific reuptake inhibitors (major anti-depressant agents such as fluoxetine or sertraline) directly activate astroglial 5-HT_{2B} receptors [136, 428] with subsequent Ca^{2+} signalling [347] or phosphorylation of extracellular regulated kinases 1/2 (ERK1/2) or up-regulation of Ca^{2+}-dependent phospholipase A2 (cPLA2) [136, 428].

Dopamine D_1, D_2, D_4 and D_5 receptors have been detected in astroglia at transcript and protein levels [245] with higher expression of D_1 [425] or D_2 receptors [23]; astrocytes from the striatum were claimed to express D_5 receptors [52]. Strong presence of D_2 receptors was found in astroglial processes enwrapping cortical interneurones [184]. Activation of D_1 and D_2 receptors in astrocytes triggers Ca^{2+} signalling originating from the $InsP_3$-induced ER Ca^{2+} release [184, 322].

Astroglia express H_1, H_2 and H_3 histamine receptors [166]. Astrocytic H_1 receptors are coupled to PLC/InsP$_3$/Ca^{2+} signalling cascade [193, 355], regulation of glucose metabolism [16] and up-regulation of EAAT2/GLT-1 plasmalemmal glutamate transporter [105]; the latter also modulated by cytosolic Ca^{2+} [377].

3.7 Bradykinin Receptors

The B_2 bradykinin receptors were identified in cultured astrocytes [71]; stimulation of these receptors induces InsP$_3$ production, Ca^{2+} signalling and glutamate release [292, 378].

3.8 Cannabinoid Receptors

Astrocytes express cannabinoid CB$_1$ receptors, which are involved in regulation of cellular metabolism [46, 340]. The CB$_1$-mediated astroglial Ca^{2+} signalling was detected in response to neuronal release of endocannabinoids [261]. Activation of CB$_1$ receptors in astroglia was also claimed to regulate neuronal synaptic plasticity [262].

3.9 Neuropeptide Receptors

V_1 vasopressin receptors induced Ca^{2+} signalling was found in cultured astrocytes and in pituicytes [129, 167]. Oxytocin receptors linked to PLC/InsP$_3$/ER Ca^{2+} release were identified in rat embryonic cultured hippocampal astrocytes [87] and in hypothalamic astrocytes [199].

ET$_A$ and ET$_B$ endothelin receptors were initially described in cultured astrocytes [147, 405]. Stimulation of ET$_{A/B}$ receptors resulted in astroglial Ca^{2+} signalling [47, 233]. In mouse cerebellar Bergmann glial cells, endothelin evoked $[Ca^{2+}]_i$ transients sensitive to the selective ET$_B$ receptor antagonist BQ-788 [399]. Activation of ET$_{A/B}$ receptors also suppresses astroglial gap junctions due to dephosphorylation of Cx43 [47, 116].

Receptors to atrial natriuretic peptide (NPR) were first identified in cultured mouse astrocytes [393]. Subsequently NPR-A [383], NPR-B [383, 438] and NPR-C [366, 383] receptors have been characterised. NPR-A and NPR-B increase intracellular cyclic guanosine monophosphate (cGMP), while NPR-C acts as a ‘clearance receptor’ that removes peptides from the extracellular space [314].

Astrocytes have been found to express δ and κ-opioid receptors [101, 102]; κ-opioid receptors induced Ca^{2+} signals sensitive to nifedipine [103], while δ-receptors, are linked to ER Ca^{2+} release [396]. Opioid receptors were claimed to regulate expression of plasmalemmal glutamate transporters [218], and astroglial growth [379].

3.10 Receptors for Leptin and Insulin

Expression of leptin receptors was detected in astrocytes in the subcommissural organ [79], in the nucleus tractus solitarius [80] and in the hypothalamus [149].

Insulin receptors have been characterised in astrocytes in vitro [131, 435]. Genetic deletion of insulin receptors from astrocytes affected brain glucose sensing, and reduced astroglial coverage of hypothalamic neurones [114]. Insulin may also act via the insulin-like growth factor 1 (IGF-1) receptor. Activation of insulin and IGF-1 receptors upregulates levels of glycogen in cultured rodent astrocytes [250].

3.11 Platelet-Activating Factor Receptor

Receptors for platelet-activating factor (1-*O*-alkyl-2-acetyl-*sn*-glycero-3-phosphocholine) were detected in astrocytes in vitro [53]. Activation of platelet-activating factor receptors stimulated production of $InsP_3$ [254, 304], induced secretion of nerve growth factor [54] and prostaglandin E_2 [391].

3.12 Protease-Activated Receptors (PAR)

Thrombin-activated PAR-1 and trypsin-activated PAR-2 receptors were found in cultured rat newborn astrocytes; activation of these receptors induced ER Ca^{2+} release [400, 401]. Astroglial PAR receptors are coupled to several signalling pathways, including stabilisation of hypoxia inducible factor-1α through ERK, JNK and PI3K/Akt cascades [436]. Activation of PAR-1 receptors (for example, by the selective peptide agonist TFLLR) is often used for selective stimulation of astroglia in situ [201, 359], although there are reports of neuronal Ca^{2+} signals triggered by the TFLLR-sensitive receptors [127].

3.13 Astroglial Membrane Transporters

3.13.1 ATP-Dependent Transporters

The most prominent and functionally important astroglial membrane P-type ATPase is represented by the Na^+-K^+ ATPase (NKA), that counter-transports Na^+ and K^+ with a stoichiometry of 3 Na^+ (expelled from the cell): 2 K^+ (imported into the cell). This defines electrogeneity of NKA. Astrocytes exclusively express α2 catalytic subunit [137, 165], which defines its peculiar properties. In contrast to neurones (which express α1 subunit) astroglial NKA is activated by physiological rises in $[K^+]_o$, while neuronal NKA is activated by an increase in $[Na^+]_i$ [134, 207, 329]. This stipulates the leading role of astroglial NKA in K^+ buffering. Astrocytes also express plasmalemmal Ca^{2+}-ATPases (PMCAs) and Sarco(Endo)Plasmic Reticulum Ca^{2+} ATP-ase (SERCA) both being responsible for Ca^{2+} homeostasis [410]. Astroglial plasma membrane and astroglial secretory vesicles possess the vacuolar V-type H^+ ATPase [288, 305].

3.13.2 Secondary Plasmalemmal Transporters of Solute Carrier (SLC) Family

3.13.2.1 Glutamate Transporters—Astrocytes represent the main sink for glutamate in the CNS [82, 410, 433]. Astrocytes express two types of plasmalemmal glutamate transporters: the excitatory amino acid transporters 1 and 2 (EAAT1/SLC1A6 and EAAT2/SLC1A2), which in rodent experiments are also referred to as GLAST1 (glutamate-aspartate transporter 1 [381]) and GLT-1 (glutamate transporter 1 [307]). The EAAT1 is predominantly expressed in the cerebellum [212], in the retina [319] and in circumventricular organs [37]; in all other parts of the brain the EAAT2 is the major type. The average density of EAAT1 is ~4700/μm^2 in Bergmann glia, and ~2300/μm^2 in the CA1 region of the hippocampus; the density of EAAT2 is ~8500/μm^2 in the hippocampus and

~740/μm^2 in the cerebellum [212]. Both transporters are concentrated in perisynaptic astroglial processes [66].

The stoichiometry of EAAT1 and EAAT2 is 3 Na^+, 1 H^+, 1 glutamate$^-$ in (glutamate is an anion at physiological conditions): 1 K^+ out [278, 426]. The equilibrium potential E_{EAAT} is the function of ions and glutamate concentration; the extracellular glutamate concentration varies between 25 nM at rest and 1 mM during synaptic transmission. The intracellular concentration of glutamate in astrocytes is ~0.3 mM due to high activity of glutamine synthetase [49, 132]. At the rest the E_{EAAT} is about +9 mV, whereas at 1 mM of glutamate in the cleft the transporter reverses at +145 mV [410]. The transporter is electrogenic and generates transmembrane current carried mainly by Na^+ ions [190, 404]. This Na^+ influx may elevate $[Na^+]_i$ by 10–30 mM [331].

Astrocytes also express the cystine/glutamate antiporter Sxc$^-$, which localises extrasynaptically [7, 70, 176]. This transporter is important for accumulation of cystine needed for production of glutathione.

3.13.2.2 Glutamine Transporters—The obligatory glutamate (and in proxy GABA) precursor glutamine is exported from astrocytes by SNAT3/SLC38A3 and SNAT5/SLC38A5 plasmalemmal glutamine transports, which are coupled with co-transport of 1 Na^+ and counter-transport of 1 H^+ [343]. Astroglial Na^+ signals stimulate glutamine efflux [397].

3.13.2.3 GABA Transporters—Astrocytes predominantly express GAT3 GABA plasmalemmal transporter with much lower expression of GAT1. The GAT3 are concentrated in astroglial processes [241, 325]. In the cerebellum GAT3 is localised in the perisynaptic processes of Bergmann glia, enwrapping inhibitory synapses [241]. In thalamic astrocytes GAT1 is concentrated in perisynaptic membranes, whereas GAT3 is localised more distantly being thus responsible for extrasynaptic GABA transport [31]. The stoichiometry of both transporters is 1 GABA: 2 Na^+: 1 Cl^-, being thus electrogenic [177, 223, 318]. The reversal potential E_{GAT} lies around −50 mV; hence, relatively small depolarisation and/or an increase in $[Na^+]_i$ favour the reverse mode operation of these transporters [402].

3.13.2.4 Glycine Transporters—Astroglial cells express GlyT1/SLC6A9 glycine plasmalemmal transporters [424]. Their stoichiometry is 1 glycine: 2 Na^+: 1 Cl^- [333]. The transporter can reverse at physiological membrane potentials [358]. This transporter-mediated glycine release was shown to be stimulated by dopamine [152].

3.13.2.5 Adenosine Transporters—Astrocytes express both equilibrative (i.e. controlled by adenosine transmembrane gradient, [187]) 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, which co-transport adenosine together with 1 Na^+ [217, 300].

3.13.2.6 Transporters for Monoamines—It seems that the main astroglial monoamine plasmalemmal transporter is represented by norepinephrine transporter NET/

SLC6A2 that couples monoamine transport with 2 Na^+ and 1 Cl^-, this transporter has higher affinity for dopamine than norepinephrine [349, 387].

3.13.2.7 D-Serine Transporters—

Transmembrane transport of D-serine in astrocytes is mediated by a neutral amino acid transporter subtype ASCT2 (SLC1A5), which is an alanine-, serine-, cysteine-preferring neutral amino acid plasmalemmal transporter [234]. The ASCT2 is a Na^+-dependent with Na^+ to amino acid stoichiometry of 1:1 [235].

3.13.2.8 Sodium-Calcium Exchangers—

All three known plasmalemmal sodium-calcium exchangers, NCX1/SLC8A1, NCX2/SLC8A2 and NCX3/SLC8A3, are expressed in astroglia [287]. The NCXs are mainly concentrated in astroglial perisynaptic processes, and co-localise with glutamate transporters and possibly with glutamate ionotropic receptors [45, 240]. The stoichiometry of astroglial NCX is 3 Na^+: 1 Ca^{2+}, and hence the equilibrium E_{NCX} lies at ~−85 to −90 mV at rest making it prone for fluctuating between forward and reverse modes [415]. Membrane depolarisation and increase in intracellular Na^+ concentration favour NCX to operate in the reverse mode, whereas increase in $[Ca^{2+}]_i$ promotes the forward mode. Operation of astroglial NCX was shown in vitro [120, 388] and in situ [189].

3.13.2.9 Sodium-Proton Exchanger, or NHE—

Astrocytes express NHE1/SLC9A1 Na^+-H^+ exchanger [69, 85] with electroneutral stoichiometry 1 Na^+ (in): 1 H^+ (out) [276]. The NHE1 is primarily responsible for efflux of protons generated by cytoplasmic metabolism and accumulated by astrocytes through glutamate uptake (each glutamate brings a single H^+ ion) and Ca^{2+} extrusion (PMCA exchanges 2 H^+ for each Ca^{2+} ion expelled).

3.13.2.10 Sodium-Bicarbonate Co-transporter, NBC—

The sodium-bicarbonate transporter NBCe1/SLC4A4 has been identified in astrocytes in culture [270] and in hippocampal slices [122]. The NBC stoichiometry is 1 Na^+: 2 HCO_3^- or 1 Na^+: 3 HCO_3^- [263], and this transporter can operate in both forward and reverse modes [394].

3.13.2.11 Sodium-Potassium-Chloride Co-transporter, NKCC1—

The Na^+-K^+-Cl-co-transporter NKCC1/SLC12A2 has been detected in Bergmann glia [170], in astrocytes from the optic nerve [227] and spinal cord [316]. It has an electroneutral stoichiometry of 1 $Na^{+:}$ 1 K^+: 2 Cl^- [226]. Experiments in situ in hippocampal slices questioned the functional role of NKCC1 in protoplasmic astrocytes in the healthy brain [207].

3.13.2.12 Glucose Transporters—

Astrocytes express the glucose transporter GLUT1/SLC2A1 [6], which is predominantly localised in endfeet and perisynaptic processes. Immunostaining revealed the presence of this transporter in grey matter astroglia [249]. It also contains GLUT4, a transporter sensitive to insulin in skeletal muscle, however the flux of glucose in astrocytes is not upregulated by insulin [250].

3.13.2.13 Monocarboxylate Transporters, MCT—

Monocarboxylate transporters 1 and 4 (MCT1/SLC16A1, MCT4/SLC16A3) provide for export of lactate from astroglial cells [126]. They may, however, mediate both export or import of lactate depending on concentration gradients for monocarboxylate and H^+ [126].

3.14 Ionic Signalling in Astroglia

3.14.1 Calcium Signalling

Discovery of astroglial Ca^{2+} signals and propagating Ca^{2+} waves [63, 76, 83, 99, 108, 185, 236] led to the formulation of the concept of astrocytic ionic signalling as a basis for their excitability [411]. Astroglial Ca^{2+} signalling depends on both intracellular and extracellular sources (Fig. 3.8) [414]. Somatic Ca^{2+} signals almost entirely depend on Ca^{2+} release from the ER mediated by $InsP_3$ receptor type 2; deletion of this channel often substantially reduced or even eliminated somatic $[Ca^{2+}]_i$ transients [4, 171, 302, 303]. At the same time, Ca^{2+} signals in astroglial processes remain even in the $InsP_3R2^{-/-}$ mice [130, 172, 375]. These signals were mediated by plasmalemmal Ca^{2+} influx [336]. This Ca^{2+} influx may reflect upon Ca^{2+} entry through ionotropic receptors and plasmalemmal channels, or Ca^{2+} influx mediated by the reverse mode of NCX [29, 361, 414].

Mechanisms underlying Ca^{2+} signalling differ between astrocytes from different brain regions. Local Ca^{2+} microdomains in Bergmann glia and in the main processes of hippocampal astrocytes were mediated solely by $InsP_3Rs$ [86, 191]. Local $[Ca^{2+}]_i$ transients in hippocampal astrocytes in contrast are mediated by TRPA1 channels [360]. In neocortical astrocytes Ca^{2+} signals involve ryanodine receptor-mediated $[Ca^{2+}]_i$-induced Ca^{2+} release [284], which is not operative in hippocampal astroglia [30]. In astrocytes in vivo sensory stimulation triggers global synchronised Ca^{2+} signals in astrocytes in somato-sensory cortex, which depend entirely on $InsP_3R2$ [171]. In cortical astrocytes spontaneous local Ca^{2+} signals in fine processes originate from Ca^{2+} release from mitochondria [3].

Global Ca^{2+} signals in the mature astrocytes in vivo are mediated by α_1-adrenoceptors [88]. Similar global astroglial signalling is observed in attention and vigilance state, when widespread astrocytic responses are evoked by acetylcholine release from projection of the nucleus basalis of Meynert and are mediated through metabotropic cholinergic receptor-$InsP_3$ pathway [67, 386]. Global astroglial Ca^{2+} signals spreading through the entire cortex were observed in response to transcranial direct current stimulation; these signals were mediated through α_1-adrenoceptors [247].

Astroglial propagating Ca^{2+} wave is mediated either by intercellular diffusion of $InsP_3$ through gap junctions [5, 143, 216] or through regenerative paracrine ATP-mediated signalling [12, 77, 128] or through the combination of both [344]. Whether propagating Ca^{2+} waves develop in the in vivo brain in awake and behaving animals remains an open question.

3.15 Sodium Signalling

The concept of astroglial Na^+ signalling has been developed rather recently [192, 331]. Physiological stimulation triggers $[Na^+]_i$ transients in astrocytes in vitro [178, 329, 330] and in situ [189, 190, 205, 328]. Generation of Na^+ signals is accomplished through plasmalemmal Na^+ entry either through plasmalemmal channels or Na^+ coupled SLC transporters, whereas extrusion of Na^+ is primarily mediated by NKA [192, 331]. Resting $[Na^+]_i$ in astrocytes is higher than in neurones, being in the range of 15–20 mM.

One of the main sources for Na^+ influx activated in response to neuronal activity is associated with operation of EAATs that co-transport 3 Na^+ with 1 glutamate; increase in extracellular glutamate may increase $[Na^+]_i$ by 10–30 mM [35, 65, 190]. Sodium influx may also be mediated by GABA transporters, ionotropic receptors, by TRP channels or by NCX operating in the forward mode [189, 205, 323]. Sodium entry may produce long-lasting $[Na^+]_i$ microdomains which, as per computational modelling, may be facilitated by fairly negative resting potential of astroglial plasmalemma [51]. Propagating Na^+ waves have been also detected in astrocytes in culture and in situ in hippocampal slices; these waves are propagating through gap junctions [206].

Astroglial Na^+ signals regulate multiple SLC transporters sensitive to transmembrane Na^+ gradients (Fig. 3.9); $[Na^+]_i$ also regulates glutamine-glutamate (GABA) shuttle through direct action on glutamine synthetase [34] and regulation of glutamine transporters [397]. Changes in $[Na^+]_i$ regulate K^+ buffering through the NKA transport and pH homeostasis by regulating NBC and NHE. By controlling reversal potential of NCX, astroglial Na^+ signals may contribute to Ca^{2+} signalling by initiating local Ca^{2+} influx in distal processes. Finally, fluctuations of $[Na^+]_i$ are coupled to astroglial metabolism, through controlling glycolysis and lactate production and possibly regulating ATP synthesis [64]. The sodium signalling system thus provides for fast coordination of neuronal activity with 'homeostatic' response of astroglia mediated through Na^+-dependent transporters, concentrated in perisynaptic processes.

3.16 Summary

Astroglial physiology is defined by a complement of ion channels, receptors for neurotransmitters, and neurohormones and membrane transporter systems. High expression of K^+ channels stabilises the membrane potential at negative level, thus ensuring electro-driving forces for operation of membrane transporters. Multiple receptors for neuroactive agents on astrocytes provide for input signals reflecting upon neuronal activity. Astrocytic ionic signalling regulates operation of transporters responsible for astroglial homeostatic response, central for astrocytic support of neuronal networks.

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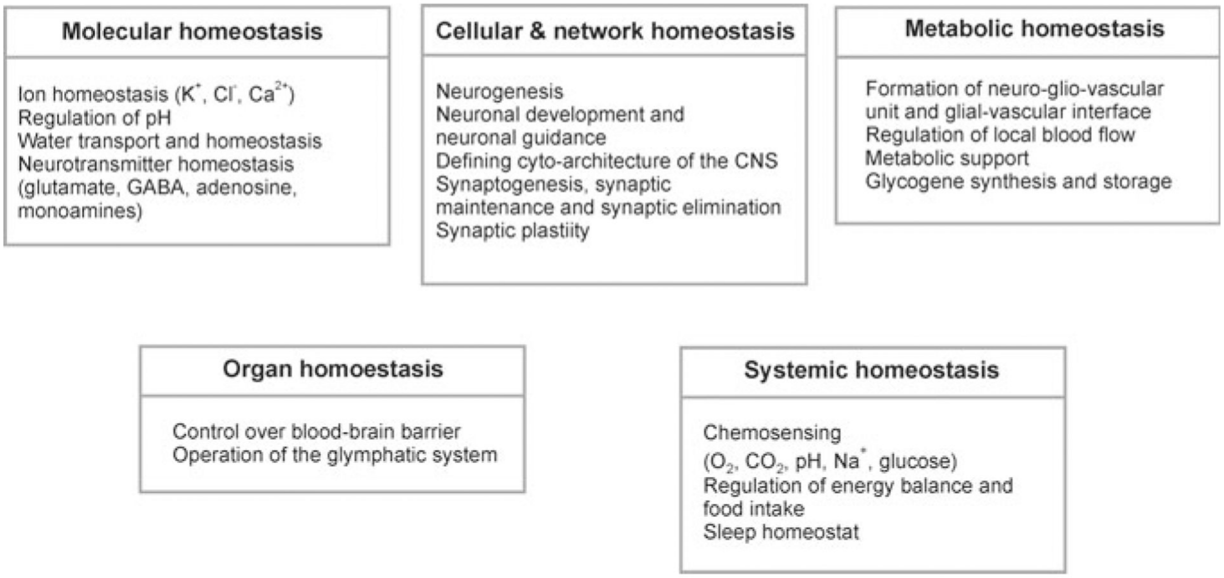

Fig. 3.1.

Homoeostatic functions of astroglia

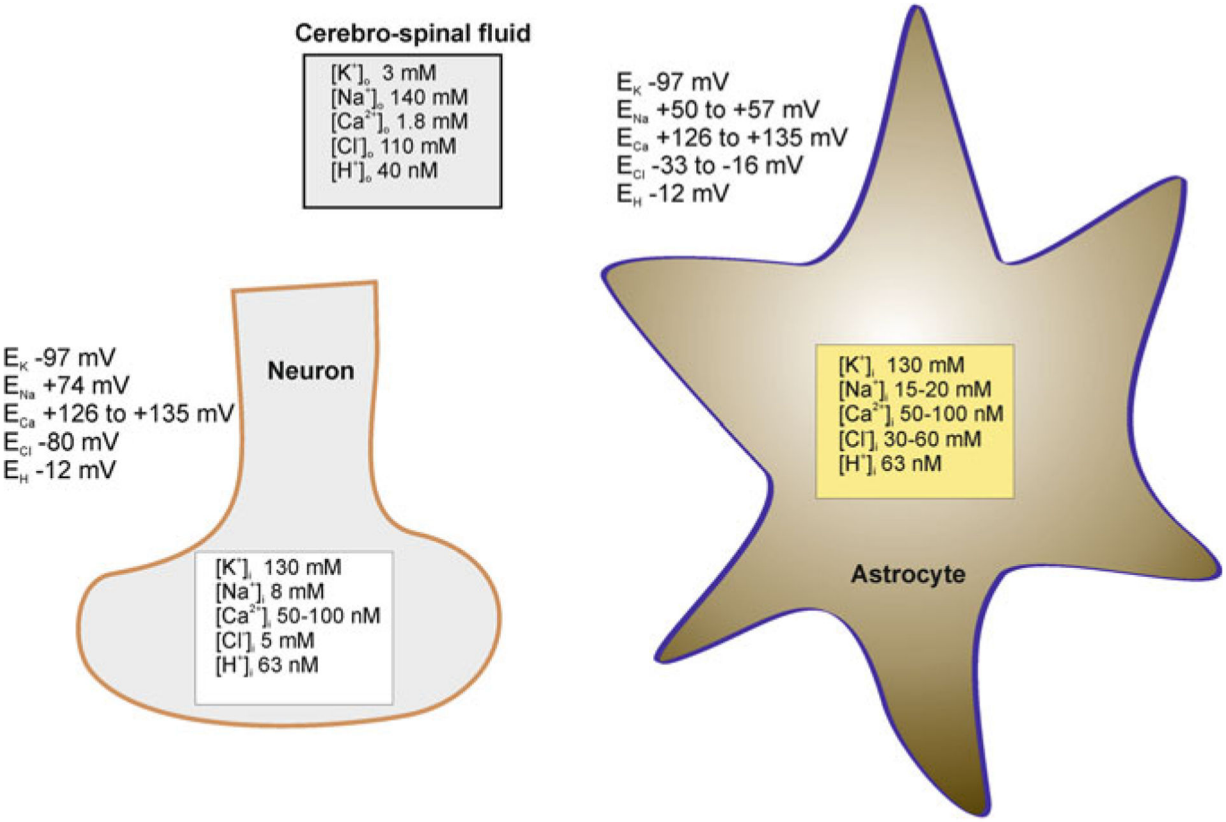

Fig. 3.2.

Ion distribution (and corresponding values of equilibrium potentials for different ions) between the cerebrospinal fluid and cytosol of astrocytes and neurones. Modified from [413]

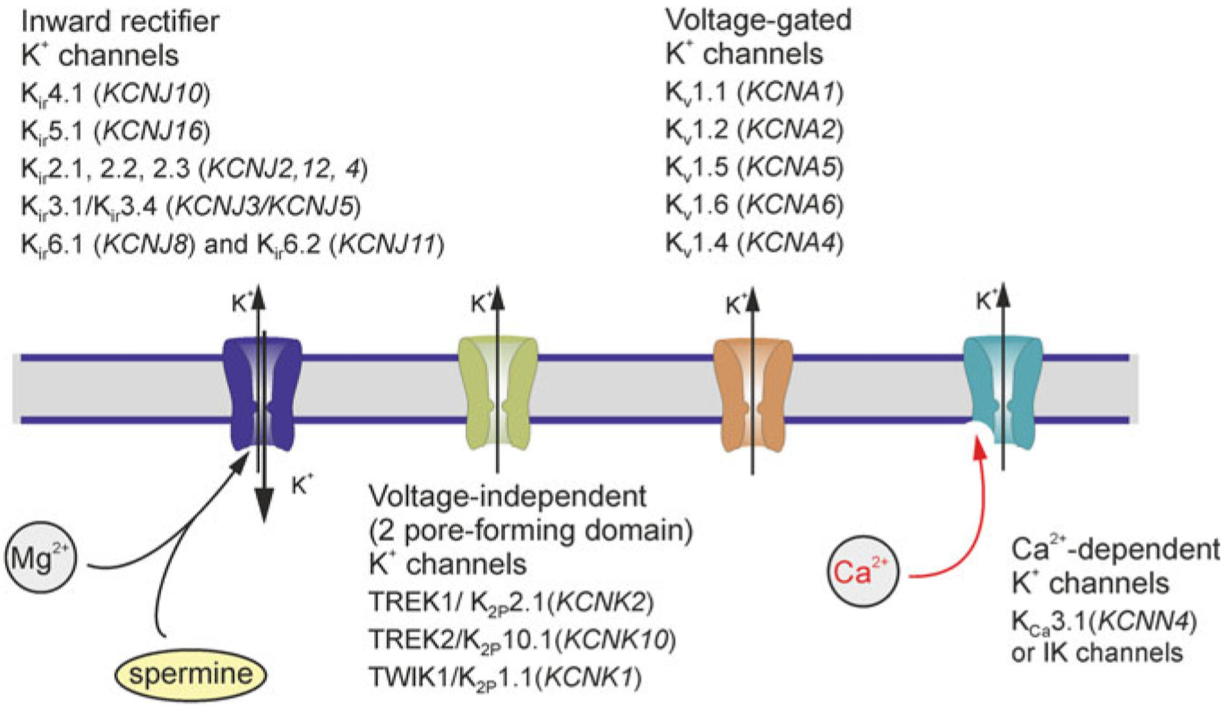

Fig. 3.3.

Potassium channels in astroglia. Gene names for a given channels are shown in parentheses. Modified from [413]

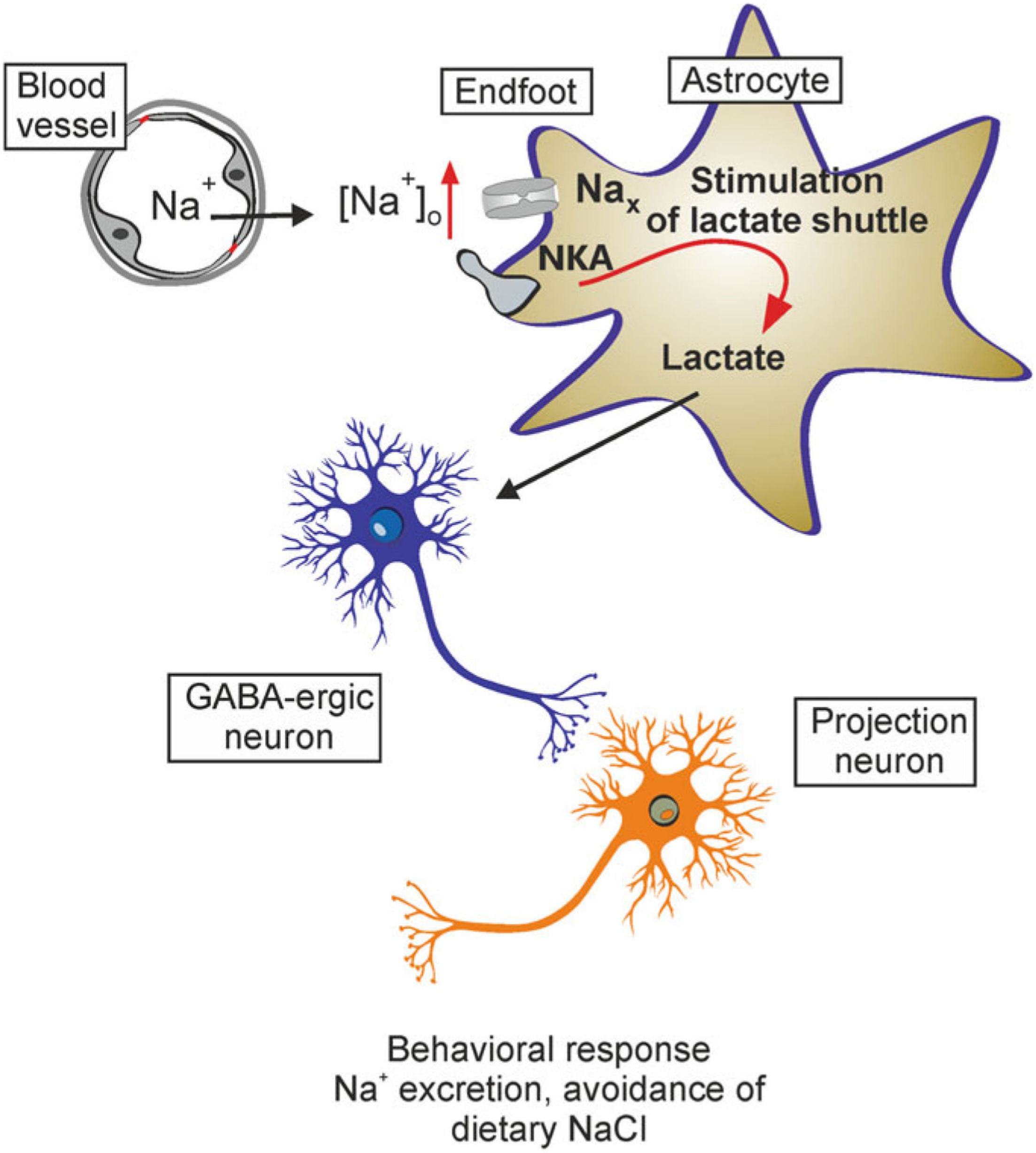

Fig. 3.4.

Astroglial Na_x channels in systemic Na^+ regulation. Increases in blood Na^+ concentration activate Na_x sodium channels localised in astrocytes residing in the subfornical organ. This leads to an increase in cytosolic Na^+ concentration, which in turn increases astroglial production of lactate. Lactate released by astrocytes is accumulated by neighbouring neurones (release and uptake carried by MCT1 in astrocytes and MCT4 in neurones, respectively), thus increasing ATP production in neurones. Increased ATP in turn closes neuronal ATP-sensitive K^+ channels, which results in depolarisation and subsequent activation of neuronal networks responsible for systemic Na^+ homeostasis. NKA, sodium-potassium ATPase. Modified from [413]

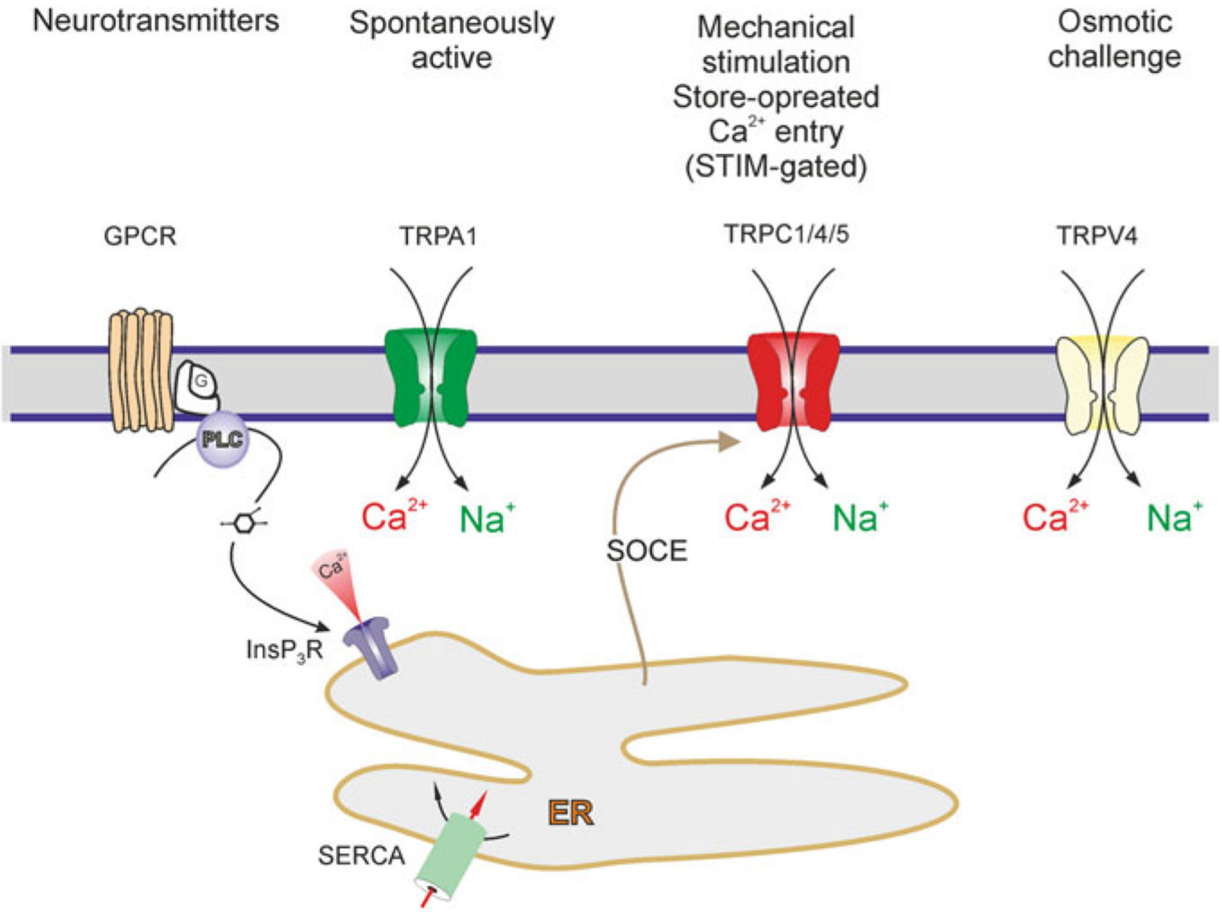

Fig. 3.5.

Astroglial TRP channels. Activation of G-protein coupled receptors (GPCR), i.e. metabotropic stimulation, can lead to production of InsP$_3$ and release of Ca^{2+} from the ER store. The Ca^{2+} content of the ER store is refilled by Sarco(Endo)Plasmic Reticulum Ca^{2+} ATPase, i.e. SERCA. Depletion of the ER Ca^{2+} store activates (via STIM) TRPC channels in astrocytes which are therefore acting as a store-operated channel, contributing to capacitative Ca^{2+} entry. Activation of all TRP channels mediates Ca^{2+} and Na^{+} influx. Modified from [413]

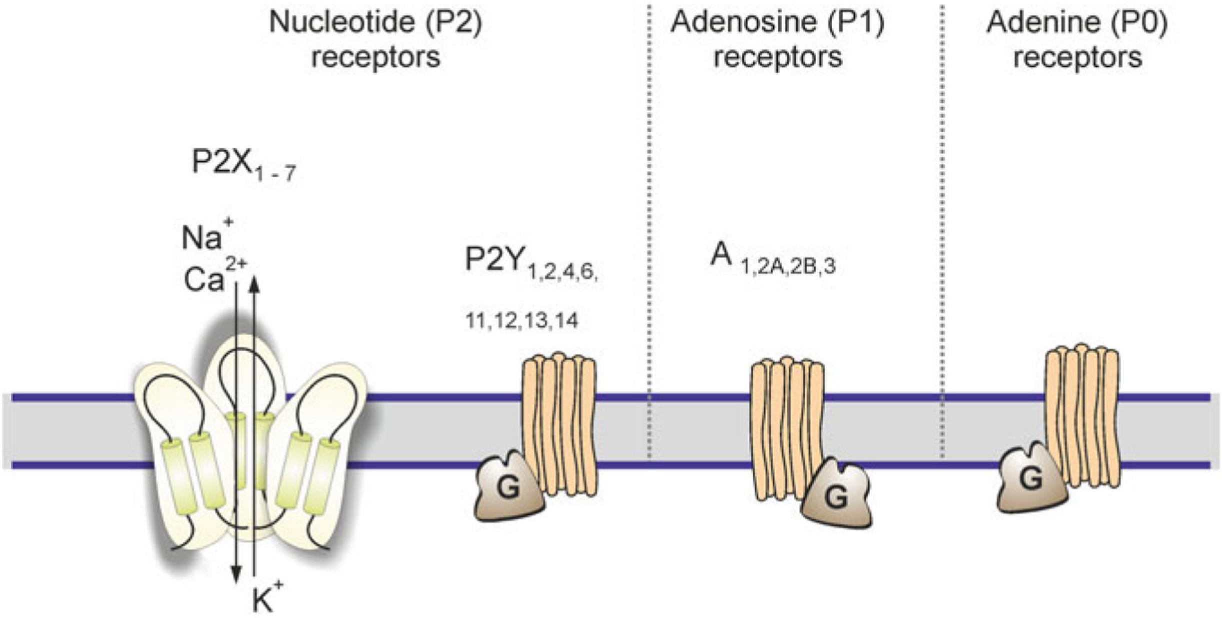

Fig. 3.6.

Classes of purinoreceptors. ATP after being released from neurones and glia is rapidly degrading by ectonucleotidases into ADP, AMP and adenosine, which act on P1 metabotropic adenosine receptors, P2X ionotropic and P2Y metabotropic nucleotide receptors. Adenine stimulates A0 adenine metabotorpic receptors, which hitherto have not been detected in astrocytes. Modified from [406]

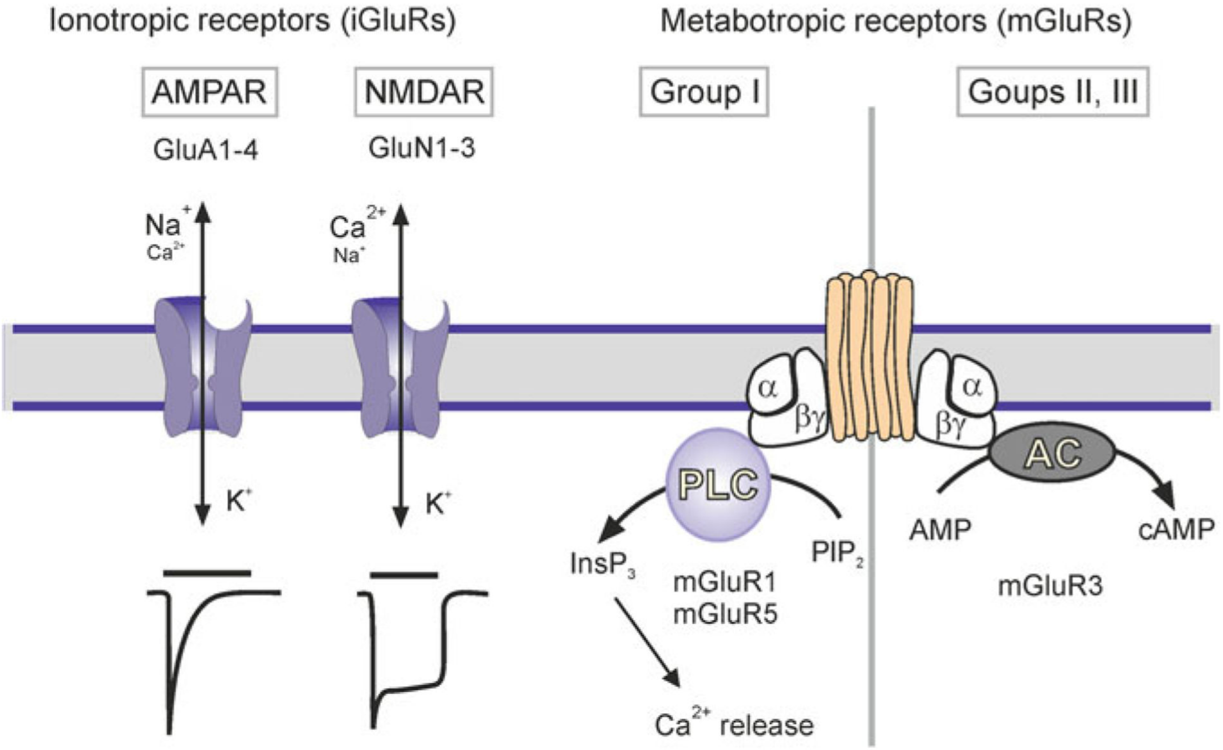

Fig. 3.7.

Classes of glutamate receptors expressed in astrocytes. Current traces show a faster time course for AMPAR than NMDAR. AC, adenylyl cyclase; AMP, adenosine monophosphate; cAMP, cyclic AMP; $InsP_3$, inositol 1,4,5-trisphosphate; PIP_2, phosphatidylinositol 4,5-bisphosphate; PLC, phospholipase C. Modified from [406]

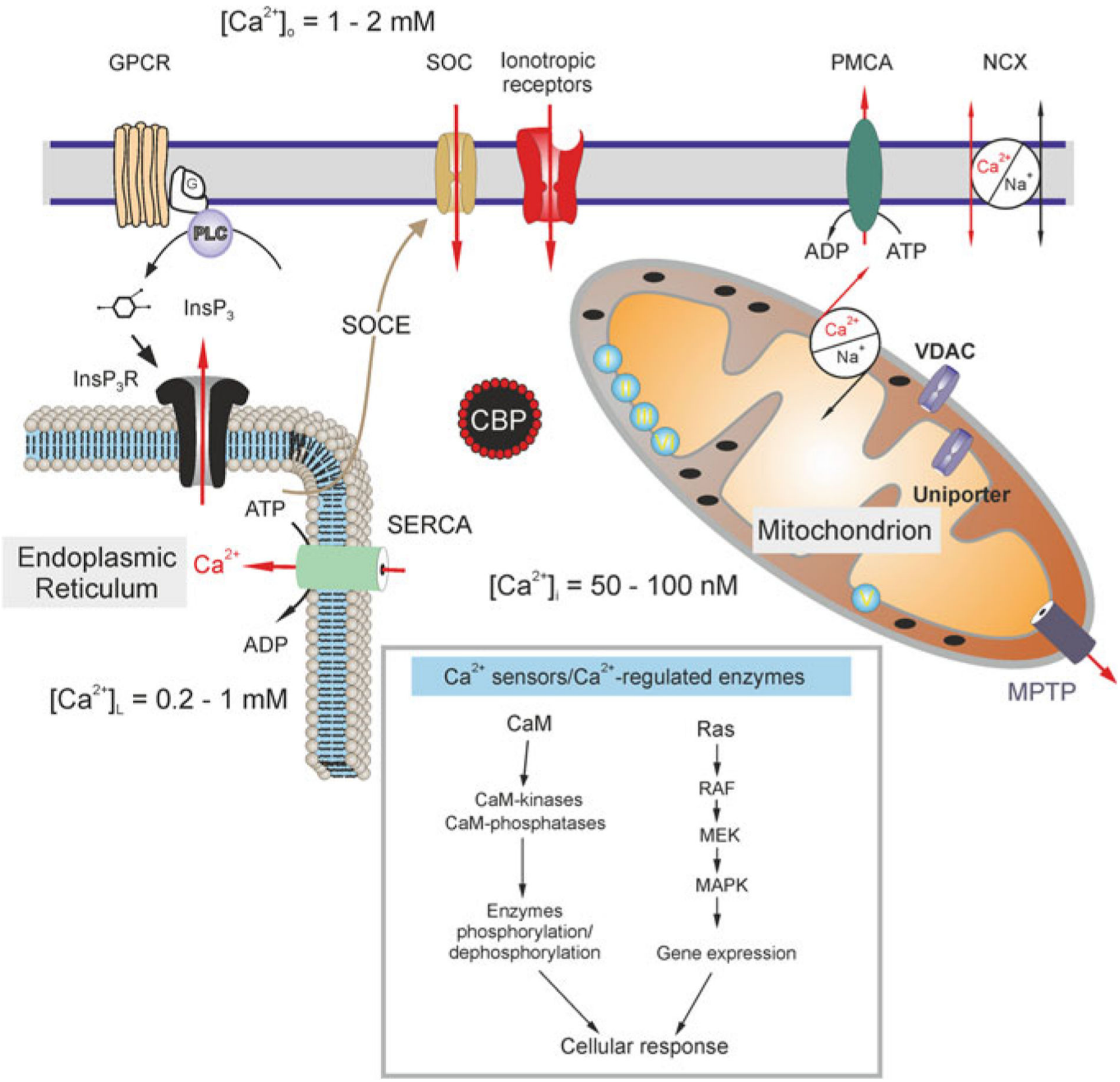

Fig. 3.8.

Calcium distribution and calcium signalling cascades in intracellular compartments. Stimuli-induced increases in $[Ca^{2+}]_i$ could be caused by the entry of Ca^{2+} from the extracellular space through ionotropic receptors or store-operated channels (SOC). Plasmalemmal Ca^{2+} pumps/ATPases (PMCA) can extrude cytosolic Ca^{2+}, while the plasmalemmal sodium-calcium exchanger (NCX) can operate in both directions depending on intercellular Na^+ concentration and membrane potential. An additional source of Ca^{2+} is available from the ER internal store that possesses inositol 1,4,5 trisphosphate ($InsP_3$) receptors, which can be activated by the activity of metabotropic G-protein coupled receptors (GPCRs) and phospholipase C (PLC). The ER store is (re)filled by the activity of the store-specific Ca^{2+}-ATPase (SERCA). Cytosolic Ca^{2+} levels can be affected by a variety of cytosolic Ca^{2+}-binding proteins (CBPs) and by the action of mitochondria. A negative membrane potential exists across the inner mitochondrial membrane. Mitochondrial Ca^{2+} uptake occurs through voltage-dependent anion channels (VDACs) present in the outer membrane and by the uniporter in the inner membrane as the electrochemical gradient drives Ca^{2+} into the matrix, while free Ca^{2+} exits the mitochondrial matrix through the mitochondrial Na^+/Ca^{2+} exchanger and transient opening of the mitochondrial permeability transition pore (MPTP). Concentrations of free Ca^{2+} in different compartments are indicated on the scheme. Inset shows various Ca^{2+} effector molecules, sensors and enzymes. CaM, calmodulin; RAF, Rapidly Accelerated Fibrosarcoma, MAPK, mitogen-activated protein kinase (MAPK), MEK, MAPK kinase. Modified from [413]

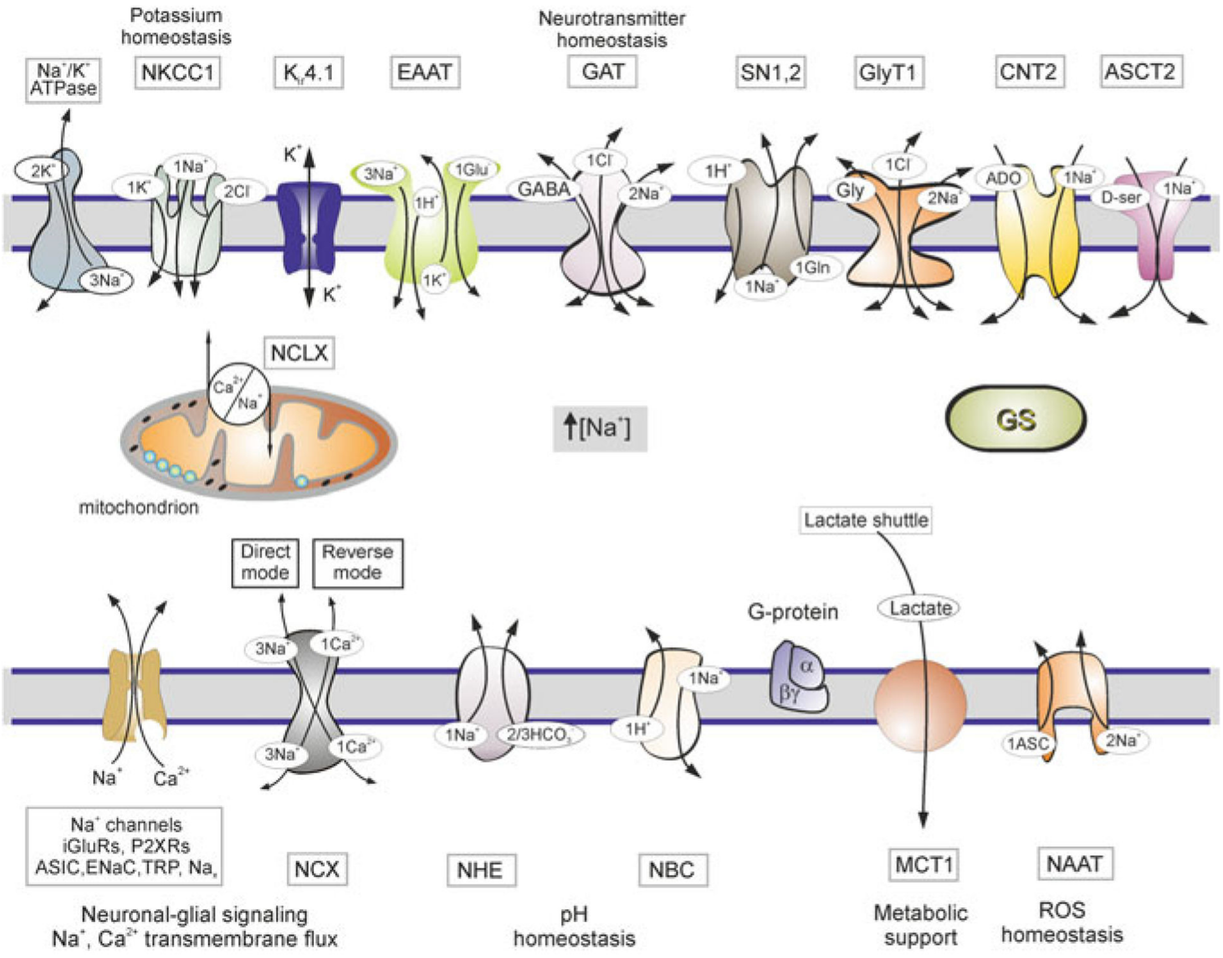

Fig. 3.9.

Molecules of Na$^+$ homeostasis and targets of Na$^+$ signalling 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 ASCT2, alanineserine-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) cotransporter; NCX-Na$^+$/Ca^{2+} exchanger; NCLX-mitochondrial Na$^+$/Ca^{2+} exchanger; NHE-Na$^+$/H$^+$ exchanger; NKCC1-Na$^+$/K$^+$/Cl$^-$ cotransporter, 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. Reactive oxygen species (ROS). Modified from [413]