Biochimica et Biophysica Acta 1813 (2011) 992–1002

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

Ionotropic receptors in neuronal–astroglial signalling: What is the role of "excitable" molecules in non-excitable cells☆

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ARTICLE INFO

Article history:
Received 21 August 2010
Received in revised form 13 September 2010
Accepted 16 September 2010
Available online 24 September 2010

Keywords:
Astrocyte
Glutamate
ATP
NMDA receptor
P2X purinoceptor
Calcium
Sodium
Synapse

ABSTRACT

Astroglial cells were long considered to serve merely as the structural and metabolic supporting cast and scenery against which the shining neurones perform their illustrious duties. Relatively recent evidence, however, indicates that astrocytes are intimately involved in many of the brain's functions. Astrocytes possess a diverse assortment of ionotropic transmitter receptors, which enable these glial cells to respond to many of the same signals that act on neurones. Ionotropic receptors mediate neurone-driven signals to astroglial cells in various brain areas including neocortex, hippocampus and cerebellum. Activation of ionotropic receptors trigger rapid signalling events in astroglia; these events, represented by local Ca^{2+} or Na^{+} signals provide the mechanism for fast neuronal–glial signalling at the synaptic level. Since astrocytes can detect chemical transmitters that are released from neurones and can release their own extracellular signals, gliotransmitters, they are intricately involved in homocellular and heterocellular signalling mechanisms in the nervous system. This article is part of a Special Issue entitled: 11th European Symposium on Calcium.

1. Introduction

Astrocytes have long been neglected as active participants in intercellular communication and information processing in the central nervous system, in part due to an initial lack of evidence for their electrical excitability. We briefly review the history of electrophysiological investigations of glial cells. The follow up is a primer on the "nuts and bolts" of astrocyte physiology. Astrocytes possess a diverse assortment of ionotropic neurotransmitter receptors, and we specifically focus on a subset of the most common pathways, the glutamatergic and purinergic signalling. Neuronal communication via synapse does not come undetected by astrocytes. Rather these glial cells can "listen" to fast synaptic transmission using their receptors and in turn can display changes in their intracellular ion concentration in particular in sodium and in calcium. Such ion excitability appears to be the trademark of astrocytic communication. It can lead to changes in the metabolic status of astrocytes and affect communication amongst themselves as well as their bi-directional communication with nearby neurones.

2. Electrophysiology of neuroglia

The role of neuroglia in the information processing in the brain remains largely unknown. In 150 years that passed after Rudolf Virchow defined the neuroglia as a "substance ... which lies between the proper nervous parts, holds them together and gives the whole its form in a greater or less degree" [1] a great deal of theories dedicated to glial functions have been in circulation. Some of the gliologists regarded neuroglia as a mere brain epithelium [2] with limited structural function. Many more theories emphasised the supportive role of glia, which form a skeleton of the nervous system, act as interneuronal insulator, provide nerve cells with nourishment, collect their waste and substitute dead neurones with a glial scar (e.g. [3–11]). Yet another group of theories regard neuroglia as a key element of neural circuitry intimately involved in information processing, regulation of synaptic transmission and ultimately in determining the cognitive potential of the brain [8,12–14].

From the very beginning of electrophysiological investigations of the brain the neuroglial cells were generally regarded as electrically non-excitable elements [2,6,15,16]. This initial view was rapidly challenged and numerous recordings have found glial depolarisation triggered by neuronal activity in various regions of the nervous system including the optic nerve [17], spinal cord [18,19] and neocortex [20–23]. Most remarkably, the glial activity could be induced by sensory stimulation. For example, depolarisation of glia in

☆ This article is part of a Special Issue entitled: 11th European Symposium on Calcium.

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doi:10.1016/j.bbamcr.2010.09.007

response to light stimulation was found in the optic nerve [17] and in the visual cortex [24]. The mechanisms of glial electrical activity remained, however, obscure and were generally attributed to extracellular accumulation of K^+ ions (for comprehensive review of early glial electrophysiology see [6]).

The simple image of neuroglia as an electrically passive element of the nervous system acting mainly as a potassium electrode has changed over last three decades. First, it has been shown that neuroglial cells express a wide spectrum of voltage-gated channels, including Na^+, Ca^{2+} K^+ and Cl^- channels ([25–32], see also [33] for comprehensive review). Second, it became obvious that neuroglia comprises many types of cells with very distinct physiological properties, and some of these cells are endowed with electrical excitability. In particular, the "fifth type" (besides astrocytes, oligodendrocytes, microglia and ependymal cells) of neuroglia, the NG2 glial cells, express relatively high densities of voltage-gated Na^+ channels and are able to generate action potentials or action-potential-like spikes [34–39]. Finally, an extensive complement of ionotropic neurotransmitter receptors was found in virtually all types of neuroglia. These receptors are activated by a synaptic release of neurotransmitters and thus mediate rapid neuronal–glial communications, although the physiological relevance of this type of signalling remains unknown.

3. Neurotransmitter receptors in glial cells

Probably the first experimental evidence demonstrating the effect of neurotransmitters on membrane potential of glial cells was obtained during intracellular microelectrode recordings from pericruciate cortical cells of anesthetised cats. These were blind recordings, which clearly recognised electrically excitable neurones and electrically passive or "unresponsive" (neuroglial) cells. A substantial fraction of these glial cells were depolarised by iontophoretic injections of γ-aminobutyric acid (GABA), and acetylcholine (ACh) [16]. Incidentally, the authors did not consider the involvement of specific receptors, suggesting that GABA and ACh action is mediated through modulation of active transport. Similarly, the microelectrode recordings from organotypic cultures prepared from medulla oblongata, pons and spinal cord have found that inhibitory amino acids GABA, glycin, β-alanine and taurine depolarised astrocytes, although this action was attributed to the release of K^+ from adjacent neurones [40].

In 1984, however, direct electrophysiological recordings from purified astroglial cell cultures have shown that excitatory and inhibitory amino acids aspartate, glutamate, GABA and glycine directly depolarised astrocytes [41,42]. The absence of neurones in these cultures excluded K^+ efflux and led to a suggestion of astroglial expression of neurotransmitter receptors. In subsequent years a great variety of neurotransmitter receptors was identified in cultured neuroglial cells (see e.g. [43–58]. With the advent of the brain/spinal cord slice preparations the functional expression of neurotransmitter receptors in glia was confirmed *in situ* [59–68]. The majority of glial receptors were of the metabotropic variety and their activation triggered cytosolic Ca^{2+} signals and glial Ca^{2+} waves that prompted the concept of glial calcium excitability [56,69,70]. At the same time, however, *in situ* experiments have proven glial expression of ionotropic receptors, represented by receptors to glutamate, ATP, GABA and glycine.

4. Ionotropic glutamate receptors in astroglia

Numerous *in situ* experiments have demonstrated functional expression of α-amino-3-hydroxy-5-methyl-isoxazole propionate (AMPA) type glutamate receptors (GluR) in astrocytes in the hippocampus [60,71] and in the cortex [72,73] as well as in cerebellar Bergmann glia [61] (Fig. 1). It is based on the expression of these receptors that hippocampal astrocytes have been categorised in two sub-types as GluR- (expressing them) and GluT- (lacking AMPA receptors) astrocytes [74]. These sub-types have distinct morphology and associated electrical properties [75,76]. It should be, however, noted that hippocampal GluT-astrocytes express metabotropic GluRs [77–80], and there is also evidence that they do express some ionotropic GluRs [81,82].

Generally, all four main subunits of AMPA receptors (GluR1–GluR4) are expressed in astroglial cells, although their combinations are different in cells from different brain regions. The hippocampal astrocytes express all four subunits with the predominant appearance of GluR2 and GluR4 subunits, which is reflected by their electrophysiology (linear I–V relation and low Ca^{2+} permeability — [71,83]). In cortical astrocytes the GluR1 and GluR4 subunits are the most abundant [84]. In Bergmann glial cells the AMPA receptors lack a GluR2 subunit which coincides with a double-rectifying I–V relationship and (relatively) high Ca^{2+} permeability [61,85]. In the spinal cord astroglia, the GluR4 immunostaining was specifically concentrated in the perivascular processes, while the somatas were positive for GluR2/3 subunits [86]. The functional expression of kainate receptors in astroglia remains doubtful, although the relevant subunits were detected at the mRNA and protein levels [86,87].

The N-methyl D-aspartate (NMDA) receptor expression in astrocytes *in situ* was initially detected by immunocytochemistry and mRNA analysis. The mRNA specific for NR1, NR2A and NR2B subunits is expressed in cerebellar Bergmann glia [88] and in cortical astroglia [89], whereas the immunoreactivity of NR1, NR2A and NR2B subunits was detected in the distal processes of cortical astrocytes [90]. Exposure of slice preparations to NMDA induced membrane currents or intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) transients in the cortical [89], in the spinal cord [91], and in a sub-population of hippocampal astrocytes [63,92]; small NMDA-induced Na^+ currents were observed in cerebellar Bergmann glial cells [93].

In astrocytes acutely isolated (with a non-enzymatic vibrodissection procedure) from mice somato-sensory cortex NMDA induced cationic currents (Fig. 1). These NMDA-induced currents were positively modulated by glycine and blocked by specific NMDA receptor antagonists MK-801 and D-2-amino-phosphonopentanoic acid (D-AP5) [72,94]. Application of glutamate to the same cells triggered the biphasic current, the components of which had a distinct pharmacological profile: the fast component was inhibited by AMPA receptor blocker 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), whereas the slow component was sensitive to D-AP5 and MK-801 (Fig. 1). The evidence favouring the expression of Ca^{2+}-permeable NMDA receptors in a sub-population of hippocampal astrocytes were gathered in Ca^{2+}-imaging experiments on acute slices [95].

The astroglial NMDA receptors differ from neuronal ones in one important property — NMDA receptors in astroglia do not exhibit voltage-dependent Mg^{2+} block. The latter is fundamental for the coincidence detecting function of neuronal NMDA receptors [96–98]. In astrocytes the NMDA-evoked currents were not affected by extracellular Mg^{2+} [72]. Incidentally, the same absence of prominent Mg^{2+} block was observed in oligodendrocytes, where both NMDA-induced currents and NMDA-triggered $[Ca^{2+}]_i$ transients were readily recorded at physiological concentrations of Mg^{2+} [99–101]. The absence of Mg^{2+} block therefore seems to be idiosyncratic for neuroglial NMDA receptors and allows their activation at negative membrane potentials characteristic for glia [94]. The molecular basis for low Mg^{2+} sensitivity of glial NMDA receptors remains unexplained; it may result, for example, from a specific expression of NR3 NMDA receptor subunits [102] or from yet unidentified posttranslational modifications of receptor subunits. Indeed, incorporation of NR3 subunit into di-meric NR1/NR3 or tri-heteromeric NR1/NR2/NR3 receptors confers low sensitivity to Mg^{2+}-block [103–105]. The di-meric NR1/NR3 receptors, however, are resistant to broad NMDA receptor agonists D-AP5 and MK-801 [103]. At the same time

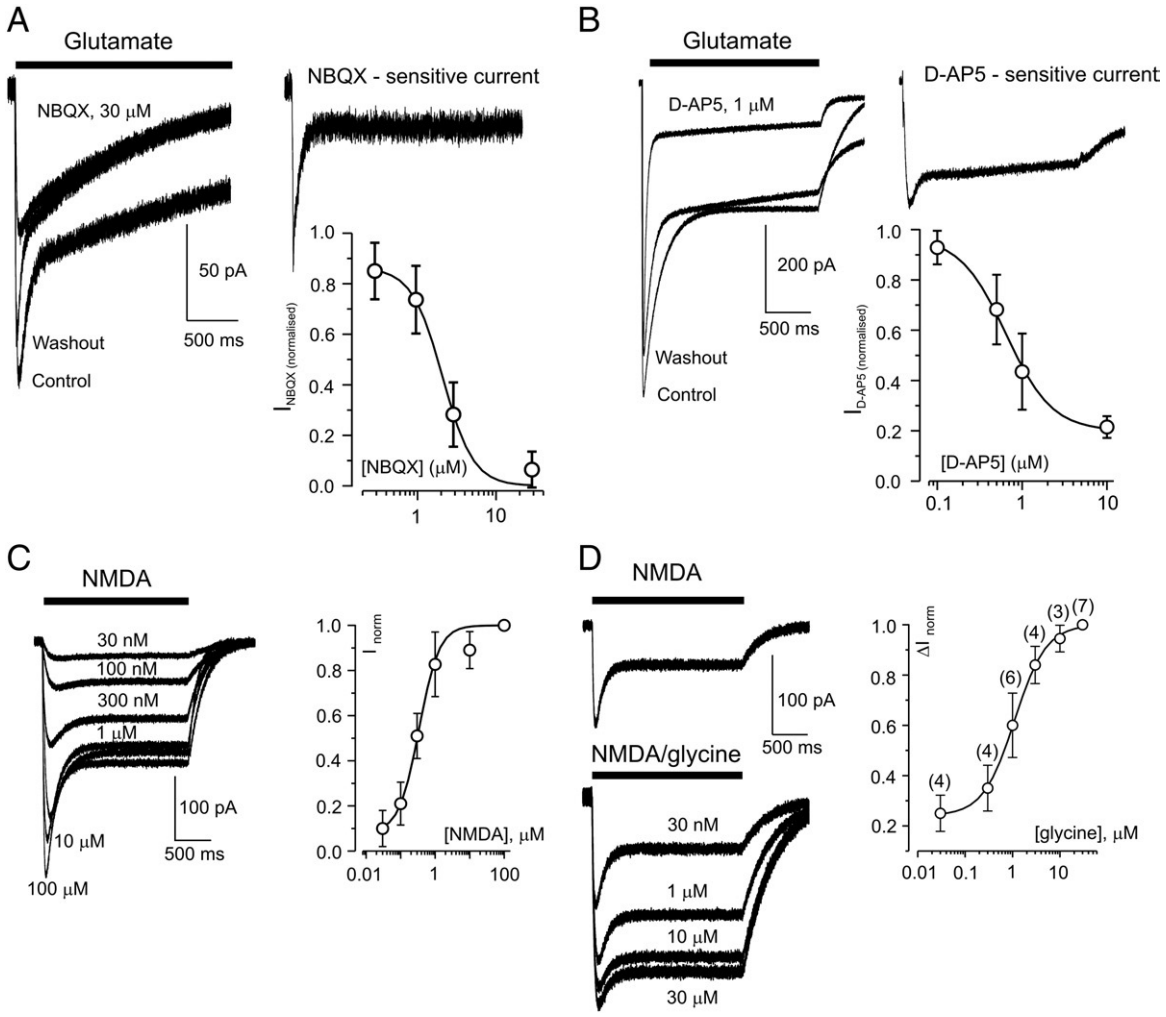

Fig. 1. AMPA and NMDA receptor-mediated currents in cortical astrocytes. A. NBQX inhibits the fast component of glutamate-induced current. Representative traces illustrate the current before, during and after application of 30 μM NBQX (left panel), and the NBQX-sensitive current obtained by subtraction (right panel). The concentration-dependence of the block of the fast component for four cells ($IC_{50} = 2.2 \pm 0.4$ μM, Hill coefficient = 1.9) is shown in the inset. B. D-AP5 inhibits the slow component of glutamate-induced current. Representative traces demonstrating the effect of 1 μM D-AP5 (left panel), and the D-AP5-sensitive component obtained by subtraction (right panel). The concentration-dependence of the block for five cells ($IC_{50} = 0.64 \pm 0.1$ μM, Hill coefficient = 1.6) in the inset. C. NMDA-induced (2 s application) currents in a single astrocyte and concentration–response curve constructed from six such experiments (EC_{50} 0.34 ± 0.06 μM, Hill coefficient = 1.5). D. Glycine-dependent potentiation of astrocyte NMDA response. NMDA-induced currents in glycine-free normal extracellular solution are shown on the top; NMDA-induced currents in the presence of different glycine concentrations (30 nM, 1 μM, 10 μM and 30 μM) are displayed below. The concentration–response curve (ΔI_{norm} represents the amplitudes of current increase normalised to the maximal increase at 30 μM glycine) constructed from seven experiments is shown on the right (EC_{50} 1.1 ± 0.07 μM, Hill coefficient = 1.2).
Reproduced with permission from [72].

astroglial NMDA receptor-mediated currents are effectively inhibited by D-AP5 and MK-801 [72], indicating the presence of NR2 subunits. Therefore the most probable composition of astroglial NMDA receptor is the tri-heteromeric assembly including two NR1, one NR2 and one NR3 subunits.

5. Ionotropic purinoceptors in astroglia

The purinergic signalling system [106,107] is abundantly present in the brain [108,109]. In physiological conditions the principal purinergic transmitter ATP is released from both neurones and neuroglia via multiple mechanisms, which include Ca^{2+}-regulated exocytosis [110,111], diffusion through high permeability plasmalemmal channels (such as hemichannels or volume-regulated anion channels [112]), and even lysosomes [113] (reviewed in [114]). The purinergic signalling system is particularly important for neuroglia, because all types of glial cells, the astrocytes, oligodendrocytes, NG2 cells and microglia express purinoceptors which control many of their vital functions [115,116].

Purinergic signalling is inherently complex due to interconversion of nucleosides (such, as adenosine and guanosine) and nucleotides (such, as ATP and GTP or corresponding dinucleotides) and their differential actions of various receptors. For example, ATP once released to the extracellular space is rapidly degraded by membrane-bound ecto-nucleotidases. The products of its extracellular hydrolysis, ADP and adenosine, can activate different plasma membrane receptors [108]. Moreover, there is cross-talk between the purinergic and glutamatergic receptor systems. Hence, guanine and adenine nucleotides can bind to the extracellular domain of ionotropic glutamate receptors causing inhibition by displacing glutamate [117–121].

The ionotropic (P2X) purinoceptors are classical ligand-gated cationic channels formed by homo- or heteromeric expression of seven distinct subunits, classified $P2X_1$ to $P2X_7$ according to a historical order of cloning [122]. The P2X receptors mediate fast synaptic transmission in neurones throughout the brain and the spinal cord [123–129]. In the astroglia expression of various P2X subunits was detected at both mRNA and protein level (see [116] for

review). Immunostaining *in situ* revealed expression of $P2X_2$, $P2X_3$ and $P2X_4$ in astrocytes in the nucleus accumbens [130]; the $P2X_1$ and $P2X_2$ receptors were found in cerebellar and spinal cord astrocytes [131,132], $P2X_{1,2,3,4,6,7}$ were identified in hippocampal astroglia [133], and $P2X_4$ receptors were detected in astrocytes from the brainstem [134].

Functional expression of ionotropic purinoceptors *in situ* was characterised in detail in cortical astrocytes that express $P2X_{1/5}$ heteromeric receptors (Fig. 2). These $P2X_{1/5}$ [73] receptors are extremely sensitive to ATP (EC_{50} for current activation ~50 nM); they display little desensitisation in the presence of the agonist and in response to the repetitive agonist applications. Astroglial receptors have also distinct pharmacology being inhibited by PPADS and TNP-ATP [73] and are subjected to modulation by phosphoinositides [135]. The P2X receptors sensitive to P2X antagonist NF023 were also found to mediate $[Ca^{2+}]_i$ transients in astrocytes from the optic nerve [136].

There are several reports about astroglial expression of $P2X_7$ receptors, the latter being specific in their very low ATP sensitivity, absence of desensitisation and ability to produce large transmembrane pores upon prolonged stimulation [122]. The $P2X_7$-mediated ion currents were, for example, observed in freshly isolated retinal Müller cells [137], in cultured astrocytes [138,139] and in some hippocampal astrocytes *in situ* [140]. In addition $P2X_7$ receptor-mediated $[Ca^{2+}]_i$ transients were observed in astroglial cells from optic nerve preparation [141]. The physiological role for $P2X_7$ receptors remains mostly unknown, although they may be involved in a variety of pathological processes involving astroglia [116].

6. Synaptic activation of astroglial ionotropic receptors

Conceptually astroglial ionotropic receptors can be activated by (i) the release of neurotransmitters from presynaptic neuronal terminals acting within the synaptic cleft or distantly through the spillover; by (ii) ectopic neurotransmitter release; by (iii) release of transmitters from glial cells or by (iv) an ambient neurotransmitter present in the interstitial space.

Initially, the spillover of glutamate released during synaptic activity was believed to be the predominant mechanism for activation of glial neurotransmitter receptors. Indeed, astroglial $[Ca^{2+}]_i$ transients and propagating calcium waves triggered by synaptically released glutamate were detected in hippocampal organotypic cultures [142], in acute hippocampal [143] and cerebellar [144] slices; in all these cases glial Ca^{2+} signalling was mediated mainly through the activation of metabotropic glutamate receptors [64,143]. Similar metabotropic-related Ca^{2+} signalling following synaptic release of acetylcholine was observed in astrocytes in hippocampal slices [145].

Neurotransmitter spillover, however, is not the only delivery mechanism of a neurotransmitter to the glial membrane. Analysis of neuronal–glial networks in different regions of the brain revealed various types of synaptoid or synapse-like contacts between neuronal terminals and glial cells. In the pituitary gland, for example, stimulation of the afferent nerve evoked typical postsynaptic responses in stellate glial cells (pituicytes); these responses were mediated through $GABA_A$ and dopamine receptors [146]. The norepiephrinergic synapse-like structures were identified in septo-hippocampal astrocytes [147]. In the recent decade direct synaptic contacts connecting neuronal afferents and NG2 glia were discovered and characterised in detail [148,149]. It turned out that majority (if not all) of NG2 positive cells in both grey and white matter receive synaptic inputs that employ GABA and glutamate as principal transmitters (see [150,151] for a comprehensive review). Electrophysiologically, stimulation of afferent nerves triggers fast postsynaptic currents in NG2 glia that result from quantal release of neurotransmitter [150].

Synaptic structures with a typical neuronal presynaptic vesicle-reach compartments apposing astroglial membranes were also detected by electron microscopy in hippocampal preparations [152]. The astroglial profiles were identified by EGFP expression (experiments were performed on transgenic animals expressing green fluorescent protein driven by GFAP promotor). Stimulation of Schaffer collaterals in acute hippocampal slices isolated from the same animals triggered GABA-mediated excitatory synaptic currents in a sub-population of astrocytes; the same astrocytes also exhibited spontaneous synaptic currents [152]. These observations further corroborated the existence of functional neuronal–astroglial synaptic contacts.

In the cortex stimulation of neuronal afferents triggered complex currents in identified (also by EGFP fluorescence) astrocytes located in layers I/II. The astroglial currents were the direct consequence of synaptic release of neurotransmitters; they were completely blocked by 1 μM of tetrodotoxin and the amplitude of astroglial currents showed the same stimulus dependence as the amplitude of synaptic currents evoked in the neighbouring neurones [72,153]. These GSC in cortical astrocytes had a complex kinetics with fast and slow components (Fig. 3A). Fast component of GSCs had a decay time τ_{fast} ~ 35 ms whereas the slow component of SCs was much slower τ_{slow} ~ 1.5 s. The GSCs were mediated by NMDA and AMPA glutamate receptors, $P2X_{1/5}$ purinoceptors and glutamate transporters; these components could be separated by appropriate pharmacological agents (Fig. 3A). Glutamate transporters mainly contributed to the slow GSCs. The AMPA glutamate receptors mediated only a minor fraction of the fast GSCs. The NMDA and P2X receptors are mainly responsible for a GSC, with $P2X_{1/5}$ having a slightly larger contribution (up to 50%) to the fast GSCs and NMDA receptors mediating a major (40–45%) fraction of slow GSCs. Spontaneous synaptic currents, (similar to miniature synaptic currents in neurones) were also readily recorded from cortical astrocytes, (Fig. 3B) indicating the close proximity of some areas of glial membranes to the sites of neurotransmitter release from the neuronal terminals. These "miniature" GSCs were mediated mostly by NMDA and P2X receptors. Thus, neocortical astrocytes demonstrate fast responses to neurotransmitters similar to postsynaptic currents thus indicating that astroglial membranes act as a postsynaptic compartment. Astrocytes receive fast quantal signals, which most likely originate from the vesicular release of glutamate and ATP from the presynaptic terminals.

The exocytosis of glutamate from neuronal terminals can also occur at the ectopic sites (the sites being located outside of the active zones of the presynaptic terminals). The ectopic glutamate release was found to dominate neuronal to Bergmann glial cell signalling in the cerebellum [154–156]. The relevance of ectopic neuronal–glial signalling in other regions of the brain seems to be less obvious. Indeed in experiments on cortical astrocytes [72] cyclothiazide (CTZ; a compound that increases the apparent affinity of AMPA receptors [157,158]) increases the AMPA-mediated component of a GSC current by 96%, which is in a good agreement with the effect of CTZ on neuronal synaptic currents [157,158]. Such an increase in astroglial currents is also similar to a twofold increase in the amplitude of response of the climbing fibre synapses on NG2 glial cells in the cerebellum [159]. In contrast, currents activated in the Bergmann glia following ectopic release exhibited more than an eightfold increase under CTZ due to the exposure of glial AMPA receptors to low concentrations of glutamate [160]. An additional similarity of GSCs in cortical astroglia to synaptically-activated currents in the NG2 cells [151] is their sustainability at repetitive stimulation (we could record GSCs for more than 40–60min at 0.5 Hz —[153]) whereas glial currents activated by ectopic release fade rapidly due to presynaptic depression and fast depletion of ectopic transmitter pools [151,155].

Conceptually however, the existence of multiple pathways and structures that maintain neuronal–glial neurochemical transmission reflects a high level of complexity and specificity in neurone–glia signalling. This high complexity is further elaborated at a molecular level as glial molecules involved in neuronal–glial transmission have a

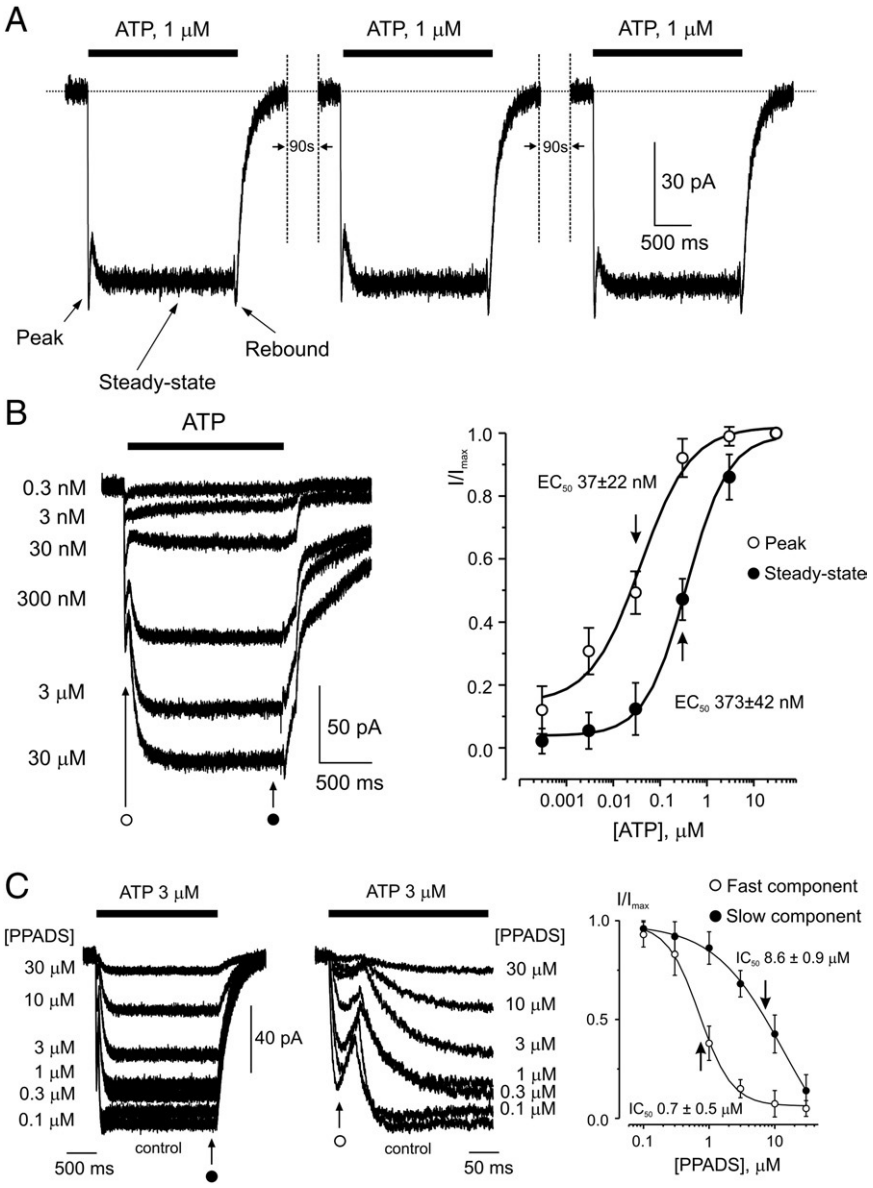

Fig. 2. $P2X_{1/5}$ receptor-mediated currents in cortical astrocytes. A. The family of ATP currents evoked by repetitive applications of the agonist. The currents show no apparent desensitisation. Current traces have a complex kinetics comprising the peak, the steady-state component and the "rebound" inward current recorded upon ATP washout as indicated on the graph. B. Concentration dependence of ATP-induced currents in cortical astrocytes. Membrane currents recorded from a single cell in response to different ATP concentrations are shown on the left. The right panel shows the concentration–response curves constructed from 9 similar experiments; current amplitudes were measured at the initial peak and at the end of the current, as indicated on the graph. C. Inhibition of ATP-induced currents by PPADS. Currents recorded at various concentrations of PPADS are shown on the left and the concentration-dependence of inhibition for peak and steady-state components constructed for 7 individual experiments is presented on the right. The peak component of the response was more sensitive to PPADS. Application of PPADS started 2 min before application of ATP. All recordings were made at a holding potential of −80 mV.
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very different sensitivity: the $P2X_{1/5}$ receptors can detect submicromolar concentrations of the agonist [73], the NMDA receptors have an EC_{50} to glutamate of 2 μM, AMPA receptors — ~50 μM, the glutamate transporters EC_{50} to glutamate varies between 5 and 70 μM, and metabotropic glutamate receptor-mediated Ca^{2+} signalling saturates at several hundred μM of glutamate [64,72,73,94,161].

7. Role of ionotropic receptors in astroglial signalling

What is the physiological significance of synaptic-like fast transmission from neuronal terminals to astroglia? It is generally accepted that neuronal and glial signalling develops in different temporal domains: fast electrical/synaptic interneuronal transmission contrasts to relatively slow astroglial Ca^{2+} waves. Within this concept the primary role in the neuronal–glial signalling was assigned to metabotropic receptors that are expressed in abundance in astrocytes. Activation of the said receptors does not necessarily require direct synaptic contacts and can be achieved either by ambient neurotransmitter or by neurotransmitter spillover. Nonetheless the morphological organisation of grey matter [162–164], divided by astrocytic territories into relatively independent functional domains, assumes numerous tight appositions between synaptic and astroglial compartments. Astroglial membranes, which cover central synapses (and thus form the tripartite synapse [165]) appear in the close vicinity to sites of neurotransmitter release from neuronal terminal and face the same concentration gradients of transmitters as neuronal postsynaptic membrane. As a result ionotropic receptors expressed in astroglial membrane can be rapidly activated by both evoked and background synaptic transmission.

Indeed, direct electrophysiological experiments (described in detail in the previous section) demonstrated that astrocytes in the neocortex

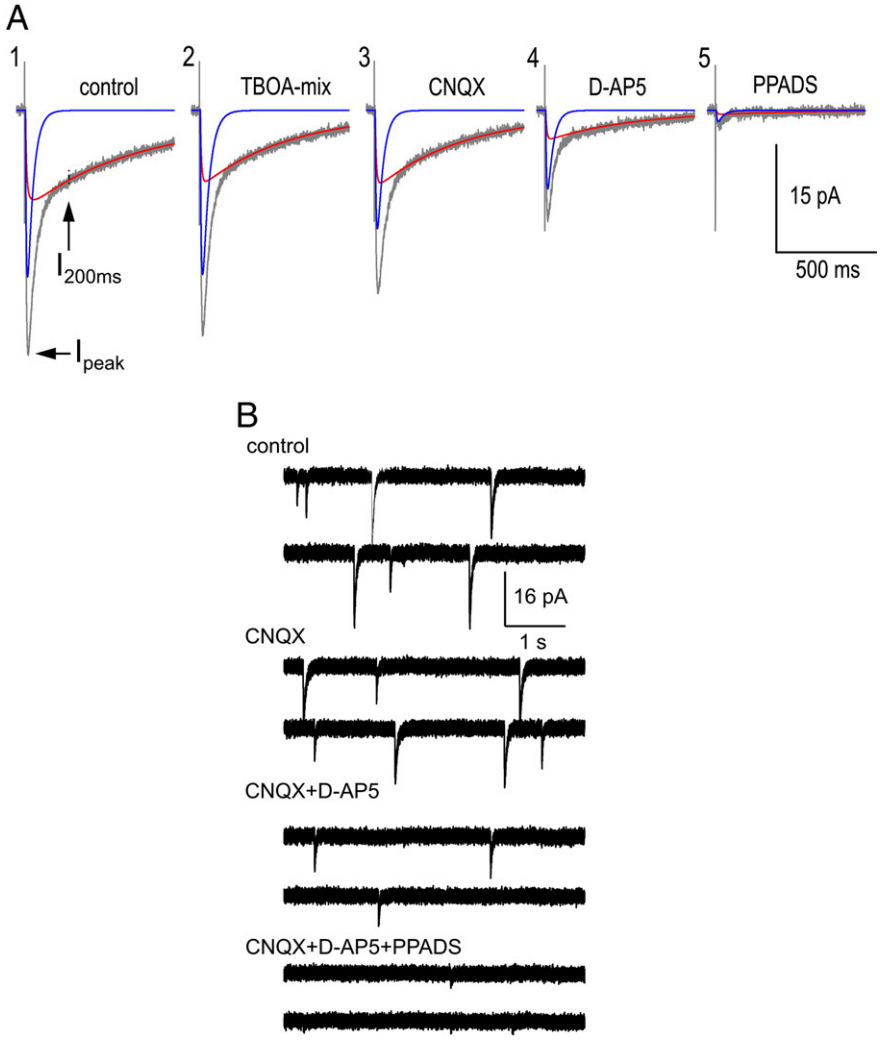

Fig. 3. Synaptically-activated currents in the cortical astrocytes. A. Transmembrane currents evoked in the astrocytes in neocortical layer II of 12 week-old mice *in situ* by stimulation of neuronal afferents were recorded in the control (1) and after consecutive application of the following pharmacological agents: (2) a combination of the antagonists of glutamate transporters TFB-TBOA, 1 μM, and DL-TBOA, 30 μM (this mixture, referred to as TBOA-mix, blocks excitatory amino-acid transporters of EAAT1–5 types); (3) a selective antagonist of AMPA receptors CNQX, 50 μM; (4) a selective antagonist of NMDA receptors, D-AP5, 30 μM and (5) the P2X receptor antagonist PPADS, 10 μM. All glial synaptically-activated currents (GSCs) were recorded at a membrane potential of −80 mV in the constant presence of 100 μM picrotoxin, stimulation frequency was 0.5 Hz. B. Miniature spontaneous currents (mGSCs) in cortical astrocytes mediated by the P2X, AMPA and NMDA receptors. Representative whole-cell recordings from the cortical astrocyte of a 12 week-old mouse in control and after consecutive applications of 50 μM CNQX, 30 μM D-AP5 and 10 μM PPADS; the NMDA and P2X receptor antagonists progressively inhibit mGSCs. All astroglial currents were recorded at a membrane potential of −80 mV in the constant presence of 100 μM picrotoxin.

[72] and in the hippocampus [152] generate excitatory currents in response to stimulation of neuronal afferents and exhibit spontaneous "miniature" currents triggered by background quantal release of neurotransmitter from the presynaptic terminal. Glial evoked and spontaneous currents have a typical pharmacology and their kinetics and biophysical properties are very similar to neuronal postsynaptic currents. In contrast to neurones, however, glial synaptic currents are always excitatory: glutamate and ATP trigger inward cationic currents, whereas GABA and glycine — outward Cl^- currents (due to relatively high cytoplasmic Cl^- concentration in astroglia which sets Cl^- reversal potential at ~−40 mV). The physiological role of fast glial excitatory synaptic currents remains unclear, as indeed, these currents cannot induce a prominent electrical response in non-excitable astrocytes; moreover they cannot even significantly depolarise an astroglial membrane due to the large K^+ conductance of the latter. The most obvious possibility therefore is that ionotropic receptors mediate local signalling associated with ion fluxes (Fig. 4). Considering that the single astrocyte in the grey matter of rodents enwraps several tens of thousands (and in human — up to 2 million) of synapses such local signalling can be physiologically important.

7.1. Ca^{2+} signalling

It is generally considered that physiological astroglial Ca^{2+} signalling is primarily driven by metabotropic G-protein-coupled receptors activated following neurotransmitter release from presynaptic terminals [166–168]. This concept has strong experimental support, because multiple metabotropic receptors are functionally expressed in astroglia, and their stimulation triggers $[Ca^{2+}]_i$ transients and propagating Ca^{2+} waves [64–66,70,80,144,169,170]. These Ca^{2+} signals result from activation of $InsP_3$-induced Ca^{2+} release from the endoplasmic reticulum, mediated primarily through type 2 $InsP_3$ receptors [171]. Calcium signals arising from activation of metabotropic receptors are believed to control exocytotic release of gliotransmitters; indeed artificial $[Ca^{2+}]_i$ transients generated in astrocytes by local Ca^{2+} uncaging, mechanical stimulation or bath application of metabotropic agonists modulated synaptic activity in Schaffer collateral–CA1 neuronal synapses [169,172–174]. Recently, however, the role of metabotropic receptors/$InsP_3$-induced Ca^{2+} signalling in astroglial physiology was questioned. Experiments on mice with genetically modified Ca^{2+} signalling pathways in astrocytes (which either overexpressed Mas-

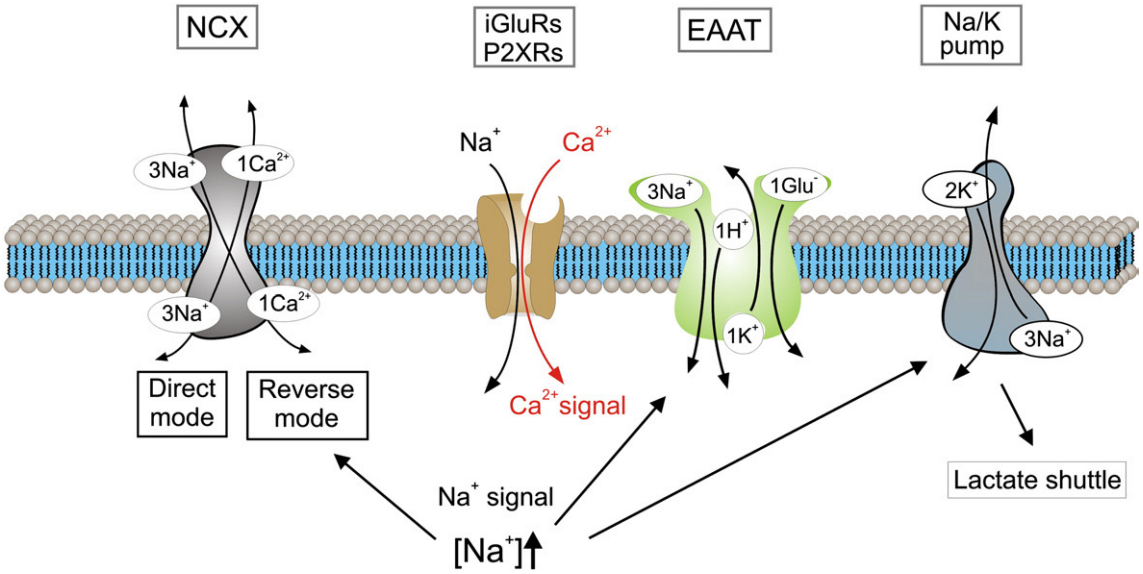

Fig. 4. Local signalling mediated by ionotropic receptors in astroglia. See text for further explanation. Abbreviations: NCX — sodium–calcium exchanger; iGluRs — ionotropic glutamate receptors; EAAT — excitatory amino acid (i.e. glutamate) transporter.

related gene A1, MrgA1, metabotropic receptor normally present only in sensory neurones, or did not express type 2 $InsP_3$ receptors [166,171,175]) have demonstrated that neither enhancement nor inhibition of astroglial metabotropic Ca^{2+} signalling affects synaptic transmission in the hippocampus.

The role for ionotropic receptors in generating astroglial Ca^{2+} signals is, however, generally neglected. This holds despite the fact that astrocytes express several sets of Ca^{2+} permeable receptors represented by AMPA/NMDA glutamate and P2X purinoceptors. Our recent data [153] demonstrated that synaptic stimulation triggers $[Ca^{2+}]_i$ increases in cortical astrocytes that are sensitive to pharmacological antagonists of NMDA and $P2X_{1/5}$ receptors. Specific inhibition of NMDA receptors by D-AP5 and $P2X_{1/5}$ receptors by NF449 reduced the amplitudes of astroglial $[Ca^{2+}]_i$ transients by 40–50%. These ionotropically induced fast astroglial $[Ca^{2+}]_i$ transients may result from direct Ca^{2+} entry through the receptor channel as well as from Ca^{2+} entry through the reversed sodium–calcium exchanger (NCX); the latter being the consequence of an increase in the cytoplasmic Na^+ concentration ($[Na^+]_i$).

7.2. Na^+ signalling

Sodium is another important ion that is redistributed upon activation of ionotropic receptors. Glutamate-induced $[Na^+]_i$ transients and propagating $[Na^+]_i$ waves were initially found in cultured astrocytes [176–179]; subsequently $[Na^+]_i$ fluctuations following exposure to glutamate or synaptic stimulation were detected in astroglial cells *in situ* in cerebellar Bergmann glia and in hippocampal astrocytes [180–182]. The levels of $[Na^+]_i$ following glutamate/synaptic stimulation could reach 10–30 mM from the basal level of ~4–5 mM [180,181,183].

It is generally believed (see [183] for comprehensive review) that astroglial $[Na^+]_i$ rises originate from the activation of Na^+-dependent glutamate transporters; the latter utilise Na^+ transmembrane gradient to move glutamate and have a stoichiometry of $3Na^+/1$ glutamate [184,185]. Indeed, inhibition of glial glutamate transporters with selective agents significantly reduces amplitudes of $[Na^+]_i$ transients triggered by exogenous glutamate and synaptic stimulation [181,183]. At the same time direct activation of ionotropic receptors can also produce substantial $[Na^+]_i$ rises. In Bergmann glial cells, for example, kainate (that activates AMPA receptors present in these cells without triggering their desensitisation) induces $[Na^+]_i$ transients with peak amplitudes ~25 mM [180,181]. In hippocampal astrocytes specific inhibition of AMPA receptors with CNQX reduced the amplitude of synaptically-activated $[Na^+]_i$ transients by ~17% [186]. In cortical astrocytes, which express poorly desensitising NMDA and $P2X_{1/5}$ receptors the contribution of ionotropic pathway to $[Na^+]_i$ elevation could be much higher, although this requires direct assessment.

The comprehension of the functional role for astroglial $[Na^+]_i$ signals is mostly speculative (Fig. 4). Nonetheless, even from the limited knowledge available it is possible to expect that these signals can be physiologically relevant. Indeed, increases in $[Na^+]_i$ are coupled to Ca^{2+} signalling through controlling forward/reverse modes of NCX; large $[Na^+]_i$ rises may induce additional Ca^{2+} influx and significantly modulate the shape of $[Ca^{2+}]_i$ transients [180]. Inhibition of NCX using benzamil indicates the participation of this exchanger in the release of homecysteic acid from astrocytes [187]. The $[Na^+]_i$ is directly coupled with $H^+/OH^-/HCO_3^-$ transport systems and thus is important for the regulation of cytoplasmic pH and acid/base homeostatic machinery [183]. The $[Na^+]_i$ controls the efficacy of astroglial uptake of neurotransmitters. The increase in $[Na^+]_i$ can significantly reduce or even reverse glutamate transporters [181,188] and relatively small elevations of $[Na^+]_i$ were reported to induce release of GABA through reversed specific transporters [189]. Finally, fluctuations of $[Na^+]_i$ can change the activity of glutamine synthetase [190] thus regulating glutamine–glutamate turnover.

The importance of intracellular Na^+ dynamics to Ca^{2+} homeostasis and signalling in astrocytes requires specific investigation. The Na^+/K^+-ATPase (type $\alpha 2$) have been colocalised with NCX in cortical astrocytes at plasma membrane–ER junctions where tightly regulated "sodium microdomains" may occur [191,192]. Incidentally, inhibition of Na^+/K^+-ATPase can generate intracellular Ca^{2+} oscillations in cultured hippocampal astrocytes [193]. In addition, subsets of mitochondria are found to closely interact with the ER [194,195]. Local $[Na^+]_i$ increases close to mitochondria–ER junctions, may directly increase the driving force for Ca^{2+} efflux from mitochondria via the mitochondrial Na^+/Ca^{2+} exchanger thus further contributing to astroglial Ca^{2+} signalling [196]. Hypothetically, this Ca^{2+} efflux could in turn activate/modulate ER Ca^{2+} release channels or NCXs.

Most importantly, however, astroglial $[Na^+]_i$ regulates lactate production and hence controls neuronal–glial lactate shuttle [197,198]. Increases in $[Na^+]_i$ activate the Na^+/K^+ pump that in turn stimulates

phosphoglycerate kinase and triggers the process of aerobic glycolysis. By the aid of this aerobic glycolysis glucose is converted into pyruvate and then into lactate in the presence of oxygen; the latter step is catalysed by lactatedehydrogenase type 5 (LDH5) exclusively expressed in astrocytes. Lactate produced by astrocytes is subsequently released into the extracellular space and is finally taken up by neurones thus providing them with energy substrate. Absolute majority of energy consumed by neurones is spent at the synaptic level [199], and it is possible to assume that local and rapid increases in astroglial $[Na^+]_i$ can initiate local metabolic support for the active synapses. This model requires localisation of $[Na^+]_i$ signals, and indeed spatially restricted $[Na^+]_i$ transients were observed in hippocampal astrocytes *in situ* [186]. Thus ionotropic receptors can regulate local metabolic support and hence control neurotransmission at a single synapse level.

8. Conclusions

Astroglial cells express several classes of fast ionotropic receptors. These receptors are activated by ongoing synaptic transmission and mediate local cytoplasmic signalling mediated through $[Ca^{2+}]_i$ and $[Na^+]_i$ transients. Rapid activation of astroglial ionotropic receptors can be instrumental for highly localised neuronal–glial signalling and integration in neuronal–glial circuitry.

Acknowledgements

Authors' research was supported by Alzheimer's Research Trust (UK) Programme Grant (ART/PG2004A/1) to AV; by the National Science Foundation (CBET 0943343) grant to VP, by the Grant Agency of the Czech Republic (GACR 305/08/1381 and GACR 305/08/1384) to AV.

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