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MINI-REVIEW

# Astrocyte and Neuron Intone Through Glutamate

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**Abstract** The unexpected finding of astrocytes to release glutamate as gliotransmitter challenges the traditional concepts on astrocyte being "passive" in CNS communications. Glutamate is the major excitatory transmitter in transferring information between neurons, but is now also known to activate astrocyte through transporters and receptors. Together with the sensitive swelling response, astrocytes could respond directly to glutamate and neuronal activity. Other new functions of astrocytes include modulation of synaptic plasticity and cerebral blood flow (CBF). The classic glutamate deplenishment through glutamine synthesis and $CO_2$ production does not account for the total glutamate internalized into astrocytes. This leads us to speculate there are many hidden functions of glutamate in neurons and astrocytes waiting to be discovered. In this review, we attempted to reexamine some of these new and older functions of glutamate and to reevaluate the roles of glutamate intoning these two cell types.

**Keywords** Glutamate · Astrocyte · Tripartite synapse · Neuronal–astrocytic communication · Swelling

## Introduction

Rudolf Virchow was the first to report glial cells in brain [1]. In 1909, Santiago Ramon ý Cajal proposed the existence of interaction between neurons and glial cells based on some histological evidence [2]. Glial cells are classified into two main groups: microglia and macroglia. Macroglia are subdivided into ependymal cells, Schwann cells, oligodendroglia and astroglia. Astrocyte is a subtype of astroglia, which outnumbers all other glial cells and is the most abundant neural cells in the brain. Unfortunately, researchers in neuroscience did not find astrocytes interesting for the greater part of a century since it was first described by Michael von Lenhossek according to their star-like shape [2]. It was only from the last few decades that research attention began to focus on the partnerships, and their collaborations at the biochemical, physiological and molecular aspects [3–5]. Currently, it is known that normal organ functions depend on a harmonious interaction among its cellular components. To better understand the normal and pathological brain functions, it is crucial for us to elucidate the intricate partnerships between astrocytes and neurons, two of the most abundant cell types in the CNS.

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When astrocytes were discovered to have glutamate receptors on their plasma membranes in 1996, we suddenly realized that glutamate, which was released from pre-synaptic neuron not only accolades excitatory signals to post-synaptic neurons (neuronal–neuronal communication), also excites astrocytes (neuronal–astrocytic communication) [6, 7]. Most important of all, the recent unexpected finding of astrocytes to release glutamate as gliotransmitter leads us to challenge the traditional concepts on astrocyte being "passive" in CNS. We now realize that communications between neural cells are no longer limited to neuronal–neuronal level, but can also be neuronal–astrocytic and astrocytic–neuronal. Based on the recent advances in the knowledge on glutamate, neurons and astrocytes, it is timely for us to reevaluate some of the new and classic roles pertaining to glutamate in the partnership of neurons and astrocytes. It is also important for us to delve into whether there are some hidden functions of glutamate being overlooked.

## Glutamate as a Gliotransmitter

Astrocyte could produce and release a variety of chemical transmitters—"gliotransmitters", e.g. glutamate, bradykinin, D-serine, PGE2, ATP, BDNF, etc. [5, 8]. Glutamate is the most studied member among these gliotransmitters. It has been shown that glutamate released during neuronal activity could activate group I mGluRs on the astrocytic plasma membrane to cause a calcium oscillation and astrocytic glutamate release to affect pre- and post-synaptic neuronal activities [9]. Xu et al. [10] confirmed the above observation that increased cytoplasmic glutamate concentration could trigger vesicle release of glutamate from astrocyte, which induced a transient inward current (SIC) in hippocampal CA1 pyramidal neurons. Astrocytes could release other gliotransmitters, e.g. ATP [11], when the non-NMDA receptors on their plasma membrane are being stimulated by glutamate released during neuronal activity. This implies that the glutamate released from astrocytes during gliotransmission would not only affect neuronal transmission, but also able to stimulate the release of gliotransmitters paracrinically and autocrinically, possible new functions of glutamate from astrocyte were not yet been proven experimentally. This recent addition of gliotransmission to the list of glutamate functions is exciting because this suggests an astrocyte involvement in information processing [12], a function formerly thought to be exclusively reserved for neurons.

## Astrocytes Use Glutamate to Affect Synaptic Plasticity

Research in the past two decades has shown that the brain has a remarkable capacity for plastic responses and is highly plastic at the level of its circuitry. Plasticity happened in synaptic remodeling, sculpting synaptic function during development and adulthood, synaptic growth after injury, as well as learning and memory formation involving long-term potentiation (LTP). Early study suggested growth factors, e.g. epidermal growth factor (EGF) and fibroblast growth factor (FGF), enhanced LTP formation [13, 14]. Some consequent researches focused on neurotrophins e.g. nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3) [15–17]. It was believed these growth factors and neurotrophins played vital roles in plasticity, which was exclusively determined by pre- and post-synaptic neurons.

More recent evidence on astrocytic involvement in the regulation of synaptic plasticity through glutamate release really extends our understanding on the complexity in the plasticity process [5, 18]. Araque et al. (1998) have shown that glutamate released from astrocyte could excite post-synaptic NMDA receptors to modulate synaptic memory [19]. The same group [20] recently observed a similar phenomenon in post-synaptic CA1 pyramidal neurons that astrocytes released glutamate to trigger NMDA receptor-mediated slow intrinsic current. Fiacco and McCarthy [9] reported in CA1 pyramidal cells that astrocytes released glutamate could increase the frequency of AMPA spontaneous EPSCs to modulate synaptic plasticity. Chou et al. [21] confirmed that astrocyte is necessary for LTP formation in post-synaptic neurons. These groundswell of supports indicated that astrocyte affects plasticity through releasing glutamate to stimulate NMDA receptor [22]. This new function of astrocytes required co-release of glutamate and D-serine, another astrocyte-derived gliotransmitter, as a co-activator for the glycine binding site on the post-synaptic NMDA receptor [23]. Now, it is generally accepted that plasticity is a result of astrocytic–neuronal interaction with glutamate playing a key role in addition to the growth and neurotropic factors described above; disregarding for some exceptional cases such as wide-spreading of calcium elevation in astrocytes of stratum radiatum did not affect neuronal calcium concentration nor their EPSC [24]. Taken together, these data shed new light on the astrocyte-glutamate-synaptic plasticity affair.

## Astrocyte Monitors Synaptic Glutamate to Regulate Synaptic Functions

Removal of glutamate from synaptic cleft after neuronal release is an essential and fundamental function of astrocytes known for many years. Previous in vitro studies in the 1980s had already shown that exogenous glutamate was mainly removed by astrocyte with a high-affinity uptake 100 times faster than neuron, suggesting termination of excitatory glutamate activity in the synapse is an astrocytic

responsibility [25, 26]. In vivo study confirmed this fact by showing that glutamate transporters on astrocyte within tripartite synapse have a similar glutamate affinity as glutamate receptors [27]. This suggested that transporters arrest synaptic glutamate with a similar velocity as glutamate binding to the receptors, and therefore compete with receptor-mediated glutamate signaling immediately after glutamate being released into the synapse. Given this new evidence, the original concept that astrocytic clearing of synaptic glutamate was only to terminate excitatory neurotransmission, now evolves into an astrocytic "monitoring" neuronal activity through regulating glutamate concentrations in the synapse. This hypothesis was confirmed by an experiment in which an increase of synaptic glutamate through inhibiting glutamate transporters with L-trans-pyrrolidine-2,4-dicarboxylic acid (L-PDC) could inhibit mEPSC in post-synaptic neuron [28]. It was further proven in glutamate transporters knock-out mice that GLT-1 and GLAST, but not EAAC1, involved in the restriction of mGluR1 in post-synaptic neuron [29].

Reagan et al. [30] believed that astrocyte triggered dendritic remodeling through their regulation of extracellular glutamate levels. Interestingly, stress could specifically increase GLT-1 expression in dentate gyrus and CA3 region of Ammon's horn, the brain area with the most prominent dendritic remodeling [31, 32]. The coincidence of synaptic glutamate concentration and dendritic remodelling between stress and astrocyte implies a possible hidden functional relationship between astrocyte and glutamate in stress. As mentioned in the previous section, it has been demonstrated that astrocyte could monitor plasticity through a release of glutamate. It will be interesting to see in the future how the plasticity response distinguishes between the glutamate released from neuron and astrocyte; in another aspect, whether the glutamate released from astrocyte and neurons play a different role in synaptic plasticity.

## Astrocytic Shape Changes in Response to Glutamate

Astrocytes are highly dynamic cells in CNS. Their extensive morphology allows them to send endfeet to make contacts with neuronal synapses, neuronal cell bodies, neighboring astrocytes and blood vessels. It has been demonstrated that astrocytes can rapidly extend and retract fine processes to engage and disengage from motile dendritic spines [33]. Dynamic structural changes in astrocytes help control the degree of neuronal–astrocytic communication at hippocampal synapses. Accumulating evidences demonstrated that change in shape of astrocytic process could modulate neuronal function [33]. This ought to involve redistribution of receptors, ion channels, etc., which ultimately modifies astrocyte to contact and interact with neighboring cells, as well as a change in CNS physiological function. The fortuitous discovery of astrocyte undergoing a transient shape change to ensheathe neurons to modulate synaptic functions during lactation [34] provides a strong evidence that astrocyte shape change involved in physiologic functions. We shall anticipate more similar observations to be identified in many more physiological changes in CNS. How astrocytes acquire the change of shape is still elusive. As for the interest of this review, we would deliberate on whether this astrocytic shape change involved glutamate.

Glutamate-mediated swelling was one of the most remarkable causes of shape changes in astrocyte. Under normal condition, astrocyte manages the CNS water homeostasis. During stroke and other injury, astrocytes are known to become edematous and modulate stroke outcome with glutamate homeostasis [35, 36]. Several in vitro studies confirmed the involvement of glutamate in astrocytic shaping that it could reduce stellation of astrocyte induced by cytochalasin B/D, dbcAMP or beta-amyloid protein [37–39], suggesting glutamate directly participates in astrocytic shape change, most likely through inducing swelling. Astrocytic swelling were found directly mediated by GLT-1 and GLAST [40]; while mGluR were not involved [41]. This suggests that swelling is an astrocytic specific response to the change in exogenous glutamate concentrations, which depends on glutamate transporters to determine how much and how fast this glutamate being internalized into the astrocyte. It has been shown that for each glutamate being internalized, there is a translocation of 436 water molecules into astrocytes [42, 43]. The rate of internalization of glutamate and water molecules directly determines the intracellular concentration of glutamate, the amount of water entry and the degree of swelling. It appears to be: the higher the neuronal activity, the larger the amount of glutamate being released, the more glutamate being internalized, and the more swollen the astrocyte going to be. We do not know whether the amount of glutamate released under normal neuronal activity could cause astrocytic swelling. However, under pathologic conditions, such as brain trauma, stroke, ischemia and epilepsy, there is tremendous amount of glutamate being released and astrocyte ought to become swollen under these conditions [44]. We should also realize that the swelling could be local, i.e., restricted to one or several endfeet, or the whole cell. It has been shown glutamate could induce subcellular organelles swelling including endoplasmic reticulum (ER) and mitochondria [45]. We have not find any evidence from the literature that glutamate effect could directly reach the nucleus of astrocytes to interfere its functions. If it does, it shall give the already intimate partnership between glutamate, astrocytes and neurons a revolutionary new look.

Addition to numerous glutamate release mechanisms in astrocyte, e.g. calcium related release, reverse transport, etc., rapid astrocytic swelling was found one of the potent ways of triggering glutamate and aspartate release from astrocyte [46]. Swelling-induced glutamate release sufficiently triggered NMDA-dependent excitotoxicity [47]. Several studies suggested that swelling-initiated glutamate release from astrocytes could exert autocrine and paracrine modulation of local brain functions [48, 49]. Furthermore, the degree of swelling in astrocyte would probably turn on respective responses, including some self-defense and protective and some known and hidden responses to allow the coping of the shift of water balance, ion homeostasis and so forth. In another words, astrocyte could possibly use glutamate internalization and degree of swelling to appraise neuronal activity. Therefore, it shall be interesting if we can correlate astrocytic swelling to glutamate concentrations and neuronal activity.

## Astrocyte Regulate Cerebral Blood Flow (CBF) in Associate with Neuronal Activity

Roy and Sherrington [50] proposed over a hundred years ago that CBF was related to neuronal activity. The recent discovery of "functional hyperemia" confirmed the association of CBF to neuronal activity and energy demand [51]. Astrocyte develops abundant ensheathing on cerebral vasculature to form blood brain barrier; therefore, it serves as an essential mediator in functional hyperemia by bridging neuronal activity and energy demand to the cerebral blood vessels.

Recent studies strongly supported the close astrocytic modulation of CBF. Astrocyte could derive and release several vasal constriction factors like PGF2$\alpha$, thromboxane A2, endothelins and 20-hydroxyeicosatetraenoic acid (20-HETE), etc. They were proposed to have essential roles for the maintenance of myogenic tone in cerebral blood vessel [5]. Contrary to vasal constriction effect, astrocytes could derive and release vasal dilation factors. Glutamate-mediated calcium oscillation in astrocyte could induce PGE2 and CO release to dilate focal blood vessel [52, 53]. Astrocyte also produces and releases other substrates including epoxyeicosatrienoic acid (EET) and cyclooxygenase COX-1 to dilate vessel [54, 55].

There is no doubt astrocyte plays a vital role in CBF regulation—both constriction and dilation. To appease "functional hyperemia", astrocyte has to provide an efficient signaling network to channel neuronal needs to the cerebral blood vessels. We are surprised that current research focused only on the classic vasal dilation/constriction factors. No published evidence could be found on glutamate and CBF regulation. Sporadic studies on kidneys have shown that glutamate could activate renal NMDA-R to modulate renal blood flow (RBF) [56, 57]. These results demonstrated that glutamate could modulate blood flow; thus it will be of great interest to investigate whether glutamate could regulate CBF, an interesting function waiting to be confirmed. It would also be essential to clarify whether a single astrocyte could perform both vasal constriction and dilation effects, or there are vasal constrictive and vasal dilatory astrocytes to coordinate CBF regulation.

Prevailing concepts stated that neurons in adult brain have very limited contact with cerebral endothelial cells. This suggested that neuron lack of direct interaction with cerebral blood vessels. Theoretically, it is hard to believe neurons only play an indirect regulation of CBF. Some conflictive evidences showed that some neurons could directly innervate cerebral vasculature and the innervations had abundant vesicles [58–60].

## Glutamate Affects Metabolism in Both Neuron and Astrocyte

Glutamate plays a key role in astrocytic and neuronal partnership. It was first shown almost 30 years ago that the uptaken glutamate was transformed into glutamine in astrocyte and exported back to neuron to replenish the glutamate release—the famous glutamate–glutamine–glutamate cycle [26, 61–65]. A recent review on metabolic fate of glutamate indicated that glutamine synthesis and $CO_2$ generation through TCA cycle are the two major outlets to deplenish these internalized glutamate [65]. Being the major excitatory signaling molecule between neurons and astrocytes, it is hard to believe that glutamate, after being internalized, serve only as metabolic substrate.

Glutamate could increase glucose utilization, lactate production, and glycogen accumulation in astrocyte through its uptake, but not its receptors [66, 67]. Interestingly, glutamate increases glucose transport and lactate production in astrocyte, but decreases glucose transport in neuron. Lactate, as one of the products from glycolysis in astrocyte, is transfered to neurons through the astrocyte–neuron lactate shuttle (ANLS) [68, 69]. Therefore, glutamate could regulate the redistribution of energy substrates among neurons and astrocyte.

## Future Challenges

A growing body of studies showed that glutamate functions as a pivotal signal between neuron and astrocyte. The examples include, but are not limited to (1) synaptic transmission; (2) synaptic plasticity; (3) monitor extracellular glutamate; (4) induce shape change in astrocyte; (5) regulate CBF and (6) modulate CNS metabolism. From these aspects we can speculate that the cell–cell interactions in CNS would be more complex than we have

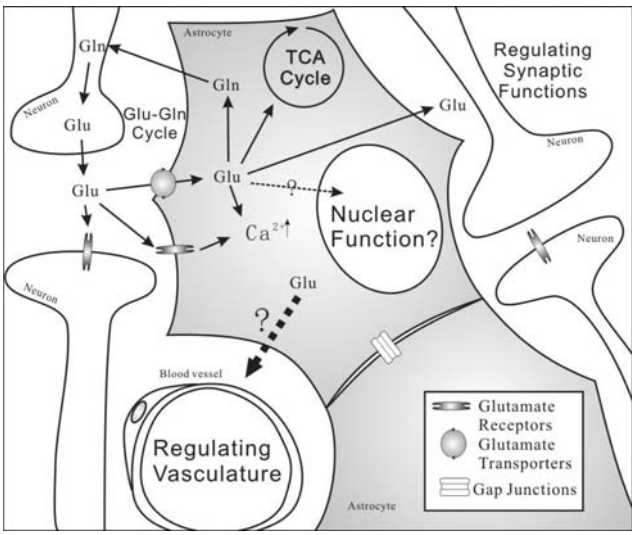


**Fig. 1** Schematic diagram of some glutamate signaling between astrocytes and neurons. Addition to mediate synaptic transmission, glutamate could be actively taken up by astrocyte, and transported back to neuron in the form of glutamine. Glutamate–glutamine cycle (Glu–Gln cycle) provides essential metabolic support to neurons. Glutamate could further trigger calcium oscillation in astrocyte, which could propagate through astrocytic gap-junctions and could induce gliotransmission, and therefore modulate synaptic functions. Astrocyte regulates vasculature to modulate CBF. From this figure, we can see interactions could be neuronal–neuronal, neuronal–astrocytic, astrocytic–neuronal and astrocytic–astrocytic, astrocytic–endothelial and so forth

imagined before. The partnership between neuron and astrocyte is not limited to neuronal–neuronal, but it could also be neuronal–astrocytic, astrocytic–neuronal, astrocytic–astrocytic, etc. (see Fig. 1). These glutamate-based signaling networks provide novel feedback and feed forward signals among these neural cells, which inevitably broaden our view on the basic CNS functions at the neuro- and gliotransmission levels.

It has been reported many years ago that internalized glutamate is synthesized into glutamine or metabolized into $CO_2$ in TCA cycle inside astrocyte, with rates of 2.4 and 7.9 nmol/min/mg protein, respectively [70]. These rates could not account for all the glutamate internalized which has a rate of 47.0 nmol/min/mg protein [70]. Furthermore, it is hard to believe that astrocyte internalizes the most important signaling molecule in the CNS only to metabolize it as an energy substrate. Our recent finding on the specific induction of nucleus swelling by internalized glutamate in astrocyte (unpublished data) sheds some light on the possible hidden function of glutamate as mentioned at the beginning of this review. We believe that the known functions of glutamate discussed in this paper are only part of the "Astrocyte and Neuron Intone through Glutamate" story, which ought to march into a very remarkably future.

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## References

1. Virchow R (1846) Uber das granulierte ansehen der Wandungen der Gerhirnventrikel. Allg Z Psychiatr 3:242–250
2. Garcia-Marin V, Garcia-Lopez P, Freire M (2007) Cajal's contributions to glia research. Trends Neurosci 30:479–487
3. Murphy TH, Blatter LA, Wier WG, Baraban JM (1993) Rapid communication between neurons and astrocytes in primary cortical cultures. J Neurosci 13:2672–2679
4. Zonta M, Carmignoto G (2002) Calcium oscillations encoding neuron-to-astrocyte communication. J Physiol Paris 96:193–198
5. Haydon PG, Carmignoto G (2006) Astrocyte control of synaptic transmission and neurovascular coupling. Physiol Rev 86:1009–1031
6. Petralia RS, Wang YX, Niedzielski AS, Wenthold RJ (1996) The metabotropic glutamate receptors, mGluR2 and mGluR3, show unique postsynaptic, presynaptic and glial localizations. Neuroscience 71:949–976
7. Petralia RS, Wang YX, Zhao HM, Wenthold RJ (1996) Ionotropic and metabotropic glutamate receptors show unique postsynaptic, presynaptic, and glial localizations in the dorsal cochlear nucleus. J Comp Neurol 372:356–383
8. Halassa MM, Fellin T, Haydon PG (2007) The tripartite synapse: roles for gliotransmission in health and disease. Trends Mol Med 13:54–63
9. Fiacco TA, McCarthy KD (2004) Intracellular astrocyte calcium waves in situ increase the frequency of spontaneous AMPA receptor currents in CA1 pyramidal neurons. J Neurosci 24:722–732
10. Xu J, Peng H, Kang N, Zhao Z, Lin JH, Stanton PK, Kang J (2007) Glutamate-induced exocytosis of glutamate from astrocytes. J Biol Chem 282:24185–24197
11. Zhang JM, Wang HK, Ye CQ, Ge W, Chen Y, Jiang ZL, Wu CP, Poo MM, Duan S (2003) ATP released by astrocytes mediates glutamatergic activity-dependent heterosynaptic suppression. Neuron 40:971–982
12. Nedergaard M, Takano T, Hansen AJ (2002) Beyond the role of glutamate as a neurotransmitter. Nat Rev Neurosci 3:748–755
13. Terlau H, Seifert W (1989) Influence of epidermal growth factor on long-term potentiation in the hippocampal slice. Brain Res 484:352–356
14. Terlau H, Seifert W (1990) Fibroblast growth factor enhances long-term potentiation in the hippocampal slice. Eur J Neurosci 2:973–977
15. Cordon-Cardo C, Tapley P, Jing SQ, Nanduri V, O'Rourke E, Lamballe F, Kovary K, Klein R, Jones KR, Reichardt LF et al (1991) The trk tyrosine protein kinase mediates the mitogenic properties of nerve growth factor and neurotrophin-3. Cell 66:173–183
16. Ip NY, Yancopoulos GD (1992) Ciliary neurotrophic factor and its receptor complex. Prog Growth Factor Res 4:139–155
17. Klein R, Nanduri V, Jing SA, Lamballe F, Tapley P, Bryant S, Cordon-Cardo C, Jones KR, Reichardt LF, Barbacid M (1991)

The trkB tyrosine protein kinase is a receptor for brain-derived neurotrophic factor and neurotrophin-3. Cell 66:395–403
18. Vernadakis A (1996) Glia–neuron intercommunications and synaptic plasticity. Prog Neurobiol 49:185–214
19. Araque A, Sanzgiri RP, Parpura V, Haydon PG (1998) Calcium elevation in astrocytes causes an NMDA receptor-dependent increase in the frequency of miniature synaptic currents in cultured hippocampal neurons. J Neurosci 18:6822–6829
20. Perea G, Araque A (2005) Synaptic regulation of the astrocyte calcium signal. J Neural Transm 112:127–135
21. Chou YC, Lin SB, Tsai LH, Tsai HI, Lin CM (2003) Cholesterol deficiency increases the vulnerability of hippocampal glia in primary culture to glutamate-induced excitotoxicity. Neurochem Int 43:197–209
22. Nestor MW, Mok LP, Tulapurkar ME, Thompson SM (2007) Plasticity of Neuron-Glial Interactions Mediated by Astrocytic EphARs. J Neurosci 27:12817–12828
23. Mustafa AK, Kim PM, Snyder SH (2004) D-Serine as a putative glial neurotransmitter. Neuron Glia Biol 1:275–281
24. Fiacco TA, Agulhon C, Taves SR, Petravicz J, Casper KB, Dong X, Chen J, McCarthy KD (2007) Selective stimulation of astrocyte calcium in situ does not affect neuronal excitatory synaptic activity. Neuron 54:611–626
25. Yu AC, Schousboe A, Hertz L (1982) Metabolic fate of 14C-labeled glutamate in astrocytes in primary cultures. J Neurochem 39:954–960
26. Hertz L, Zielke HR (2004) Astrocytic control of glutamatergic activity: astrocytes as stars of the show. Trends Neurosci 27:735–743
27. Huang YH, Bergles DE (2004) Glutamate transporters bring competition to the synapse. Curr Opin Neurobiol 14:346–352
28. Oliet SH, Piet R, Poulain DA (2001) Control of glutamate clearance and synaptic efficacy by glial coverage of neurons. Science 292:923–926
29. Huang YH, Sinha SR, Tanaka K, Rothstein JD, Bergles DE (2004) Astrocyte glutamate transporters regulate metabotropic glutamate receptor-mediated excitation of hippocampal interneurons. J Neurosci 24:4551–4559
30. Reagan LP, Rosell DR, Wood GE, Spedding M, Munoz C, Rothstein J, McEwen BS (2004) Chronic restraint stress up-regulates GLT–1 mRNA and protein expression in the rat hippocampus: reversal by tianeptine. Proc Natl Acad Sci USA 101:2179–2184
31. Pham K, Nacher J, Hof PR, McEwen BS (2003) Repeated restraint stress suppresses neurogenesis and induces biphasic PSA-NCAM expression in the adult rat dentate gyrus. Eur J Neurosci 17:879–886
32. McEwen BS (1999) Stress and hippocampal plasticity. Annu Rev Neurosci 22:105–122
33. Haber M, Zhou L, Murai KK (2006) Cooperative astrocyte and dendritic spine dynamics at hippocampal excitatory synapses. J Neurosci 26:8881–8891
34. Oliet SH, Panatier A, Piet R (2006) Functional neuronal-glial anatomical remodelling in the hypothalamus. Novartis Found Symp 276:238–248 discussion 248–252, 275–281
35. Barron KD, Dentinger MP, Kimelberg HK, Nelson LR, Bourke RS, Keegan S, Mankes R, Cragoe EJ Jr (1988) Ultrastructural features of a brain injury model in cat. I. Vascular and neuroglial changes and the prevention of astroglial swelling by a fluorenyl (aryloxy) alkanoic acid derivative (L-644,711). Acta Neuropathol 75:295–307
36. Jenkins LW, Povlishock JT, Becker DP, Miller JD, Sullivan HG (1979) Complete cerebral ischemia. An ultrastructural study. Acta Neuropathol 48:113–125
37. Abe K, Saito H (2000) L-glutamate suppresses amyloid beta-protein-induced stellation of cultured rat cortical astrocytes. J Neurochem 74:280–286
38. Abe K, Saito H (2001a) Na + and K + dependence of L-glutamate-induced suppression of astrocyte stellation in culture. Biol Pharm Bull 24:50–53
39. Abe K, Saito H (2001b) L-glutamate suppresses astrocyte stellation induced by actin breakdown in culture. Biol Pharm Bull 24:347–350
40. Kimelberg HK, Rose JW, Barron KD, Waniewski RA, Cragoe EJ (1989) Astrocytic swelling in traumatic-hypoxic brain injury. Beneficial effects of an inhibitor of anion exchange transport and glutamate uptake in glial cells. Mol Chem Neuropathol 11:1–31
41. Weiczner R, Krisztin-Peva B, Mihaly A (2007) Blockade of AMPA-receptors attenuates 4-aminopyridine seizures, decreases the activation of inhibitory neurons but is ineffective against seizure-related astrocytic swelling. Epilepsy Res 78:22–32
42. MacAulay N, Gether U, Klaeke DA, Zeuthen T (2002) Passive water and urea permeability of a human Na(+)-glutamate cotransporter expressed in Xenopus oocytes. J Physiol 542:817–828
43. MacAulay N, Gether U, Klaerke DA, Zeuthen T (2001) Water transport by the human Na+-coupled glutamate cotransporter expressed in Xenopus oocytes. J Physiol 530:367–378
44. Swanson RA, Ying W, Kauppinen TM (2004) Astrocyte influences on ischemic neuronal death. Curr Mol Med 4:193–205
45. Brustovetsky N, Brustovetsky T, Jemmerson R, Dubinsky JM (2002) Calcium-induced cytochrome c release from CNS mitochondria is associated with the permeability transition and rupture of the outer membrane. J Neurochem 80:207–218
46. Kimelberg HK (2004) Increased release of excitatory amino acids by the actions of ATP and peroxynitrite on volume-regulated anion channels (VRACs) in astrocytes. Neurochem Int 45:511–519
47. Haussinger D, Schliess F (2005) Astrocyte swelling and protein tyrosine nitration in hepatic encephalopathy. Neurochem Int 47:64–70
48. Kimelberg HK, Goderie SK, Higman S, Pang S, Waniewski RA (1990) Swelling-induced release of glutamate, aspartate, and taurine from astrocyte cultures. J Neurosci 10:1583–1591
49. Pangrsic T, Potokar M, Haydon PG, Zorec R, Kreft M (2006) Astrocyte swelling leads to membrane unfolding, not membrane insertion. J Neurochem 99:514–523
50. Roy CS, Sherrington CS (1890) On the regulation of the blood-supply of the Brain. J Physiol 11:85–108
51. Zonta M, Angulo MC, Gobbo S, Rosengarten B, Hossmann KA, Pozzan T, Carmignoto G (2003) Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation. Nat Neurosci 6:43–50
52. Zonta M, Sebelin A, Gobbo S, Fellin T, Pozzan T, Carmignoto G (2003) Glutamate-mediated cytosolic calcium oscillations regulate a pulsatile prostaglandin release from cultured rat astrocytes. J Physiol 553:407–414
53. Li A, Xi Q, Umstot ES, Bellner L, Schwartzman ML, Jaggar JH, Leffler CW (2008) Astrocyte-derived CO is a diffusible messenger that mediates glutamate-induced cerebral arteriolar dilation by activating smooth muscle Cell KCa channels. Circ Res 102:234–241
54. Bennett MR, Farnell L, Gibson WG (2008) Origins of blood volume change due to glutamatergic synaptic activity at astrocytes abutting on arteriolar smooth muscle cells. J Theor Biol 250:172–185
55. Takano T, Tian GF, Peng W, Lou N, Libionka W, Han X, Nedergaard M (2006) Astrocyte-mediated control of cerebral blood flow. Nat Neurosci 9:260–267

56. Deng A, Valdivielso JM, Munger KA, Blantz RC, Thomson SC (2002) Vasodilatory N-methyl-D-aspartate receptors are constitutively expressed in rat kidney. J Am Soc Nephrol 13:1381–1384
57. Yang CC, Chien CT, Wu MH, Ma MC, Chen CF (2008) NMDA receptor blocker ameliorates ischemia/reperfusion-induced renal dysfunction in rat kidneys. Am J Physiol Renal Physiol 0:00481.2007v1
58. Issidorides MR (1971) Neuronal vascular relationships in the zona compacta of normal and parkinsonian substantia nigra. Brain Res 25:289–299
59. Cohen Z, Molinatti G, Hamel E (1997) Astroglial and vascular interactions of noradrenaline terminals in the rat cerebral cortex. J Cereb Blood Flow Metab 17:894–904
60. Zlokovic BV (2008) The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron 57:178–201
61. Schousboe A, Svenneby G, Hertz L (1977) Uptake and metabolism of glutamate in astrocytes cultured from dissociated mouse brain hemispheres. J Neurochem 29:999–1005
62. Hertz L, Schousboe A, Boechler N, Mukerji S, Fedoroff S (1978) Kinetic characteristics of the glutamate uptake into normal astrocytes in cultures. Neurochem Res 3:1–14
63. Yu AC, Schousboe A, Hertz L (1984) Influence of pathological concentrations of ammonia on metabolic fate of 14C-labeled glutamate in astrocytes in primary cultures. J Neurochem 42: 594–597
64. Hertz L, Peng L, Dienel GA (2007) Energy metabolism in astrocytes: high rate of oxidative metabolism and spatiotemporal dependence on glycolysis/glycogenolysis. J Cereb Blood Flow Metab 27:219–249
65. McKenna MC (2007) The glutamate-glutamine cycle is not stoichiometric: fates of glutamate in brain. J Neurosci Res 85:3347–3358
66. Pellerin L, Magistretti PJ (1994) Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. Proc Natl Acad Sci USA 91:10625–10629
67. Swanson RA, Yu AC, Chan PH, Sharp FR (1990) Glutamate increases glycogen content and reduces glucose utilization in primary astrocyte culture. J Neurochem 54:490–496
68. Pellerin L, Bouzier-Sore AK, Aubert A, Serres S, Merle M, Costalat R, Magistretti PJ (2007) Activity-dependent regulation of energy metabolism by astrocytes: an update. Glia 55:1251–1262
69. Chih CP, Roberts EL Jr (2003) Energy substrates for neurons during neural activity: a critical review of the astrocyte-neuron lactate shuttle hypothesis. J Cereb Blood Flow Metab 23:1263–1281
70. Hertz L, Swanson RA, Newman GC, Marrif H, Juurlink BH, Peng L (1998) Can experimental conditions explain the discrepancy over glutamate stimulation of aerobic glycolysis? Dev Neurosci 20:339–347