

Astrocytes Control Neuronal Excitability in the Nucleus Accumbens

Tommaso Fellin¹, Marcello D'Ascenzo², and Philip G. Haydon^{1,*}

¹Department of Neuroscience, University of Pennsylvania School of Medicine, Philadelphia, PA 19104; ²Institute of Human Physiology, Catholic University, Largo Francesco Vito 1, 00168 Roma, Italy

E-mail: tfellin@mail.med.upenn.edu; dascenzo@rm.unicatt.it; pghaydon@mail.med.upenn.edu

Received June 22, 2007; Revised July 6, 2007; Accepted July 9, 2007; Published November 2, 2007

Though accumulating evidence shows that the metabotropic glutamate receptor 5 (mGluR5) mediates some of the actions of extracellular glutamate after cocaine use, the cellular events underlying this action are poorly understood. In this review, we will discuss recent results showing that mGluR5 receptors are key regulators of astrocyte activity. Synaptic release of glutamate activates mGluR5 expressed in perisynaptic astrocytes and generates intense Ca^{2+} signaling in these cells. Ca^{2+} oscillations, in turn, trigger the release from astrocytes of the gliotransmitter glutamate, which modulates neuronal excitability by activating NMDA receptors. By integrating these results with the most recent evidence demonstrating the importance of astrocytes in the regulation of neuronal excitability, we propose that astrocytes are involved in mediating some of the mGluR5-dependent drug-induced behaviors.

KEYWORDS: glia, astrocytes, glutamate release, gliotransmission, glutamate, metabotropic glutamate receptors, neuronal excitability, medium spiny neurons, drug addiction

INTRODUCTION

During the past 20 years, there has been a revolution in our understanding of the active roles of astrocytes. Although we initially knew that they played pivotal roles in performing metabolic functions, in taking up elevated K^+ , and in clearing synaptic transmitters, we now appreciate that astrocytes can release chemical transmitters through a process called gliotransmission, which modulates neighboring neurons [1,2]. At this point, we therefore understand that astrocytes are active signaling elements in the nervous system, although we do not yet appreciate their roles in neuronal network function, behavior, or whether alterations in the basic biology of the astrocyte and gliotransmission could lead to long-term changes in nervous system function.

Our goal is to review some of the basic biological breakthroughs that have led to our new appreciation of glial function, and then integrate this knowledge into potential functions in reward centers of the brain to illuminate how glia might play important roles in responding to drugs of abuse, including cocaine and alcohol. With the development of molecular genetic tools to perturb the astrocyte selectively, the stage is now set for future studies to determine whether and how astrocytes contribute to both the function and dysfunction of the nervous system.

*Corresponding author.

©2007 with author.

Published by TheScientificWorld; www.thescientificworld.com

ASTROCYTES ARE EXCITABLE

Electrical recordings from astrocytes show that they have a very negative resting potential, low input resistance, high resting conductance that is selective for K^+ , and they are electrically unexcitable. Consequently, little attention has been focused on these cells during the past century, given that it was determined early in the 20th century that electrical excitability is a fundamental property of the nervous system that is essential for mediation of behavior. However, in the early 1990s, the development of ion-selective indicators and advanced forms of microscopy allowed a re-examination of astrocyte excitability. Initially in cell culture[3,4], and later *in situ*[5,6] and *in vivo*[7], Ca^{2+} imaging demonstrated that astrocytes respond to the application of chemical transmitters with an elevation of their internal Ca^{2+} levels. Given that astrocytes are not electrically excitable, it was rapidly realized that voltage-gated Ca^{2+} conductances could not mediate Ca^{2+} accumulations, rather that IP_3 -gated release of Ca^{2+} from internal stores was the prevalent source of Ca^{2+} that mediated Ca^{2+} oscillations observed in astrocytes[2]. More recent studies show that the stimulation of presynaptic axons in brain slice preparations evokes Ca^{2+} oscillations in astrocytes, and that sensory stimulation *in vivo* is able to activate this form of excitability within these non-neuronal cells[8]. Typically spontaneous and activity-evoked Ca^{2+} signals in astrocytes *in situ*[5,9,10] as well as *in vivo*[7] display an oscillatory pattern consisting of repetitive Ca^{2+} spikes, which we will refer to in the rest of the manuscript as Ca^{2+} oscillations.

A hallmark of neuronal function is the use of ligand-gated ion channels to cause rapid neuronal depolarizations in response to the release of synaptic transmitters. Though astrocytes can express such receptors, more typically it is the metabotropic receptors that respond to synaptic transmitters. For example, following stimulation of the Schaffer collaterals in the hippocampus, the transmitter that spills over from the synaptic cleft activates a combination of metabotropic glutamate and purinergic receptors to induce the release of Ca^{2+} from IP_3 -sensitive Ca^{2+} stores within astrocytes[11]. Astrocytes express a plethora of metabotropic receptors[2] and, as will be discussed later, one of particular interest is metabotropic glutamate receptor 5 (mGluR5).

GLIOTRANSMISSION: THE RELEASE OF CHEMICAL TRANSMITTERS FROM ASTROCYTES

After the initial observations of Ca^{2+} excitability within astrocytes, it was not long until at least one of the consequences of these Ca^{2+} signals was identified. As has been typical for this field, initial observations in cell cultures, then later in brain slice preparations, showed that a Ca^{2+} elevation within the astrocyte was necessary and sufficient for the release of chemical transmitter from an astrocyte. The application of bradykinin, which mobilizes Ca^{2+} from the internal stores of astrocytes, caused glutamate to be released from purified cultures of astrocytes[12]. This process of glutamate release critically requires elevations of internal Ca^{2+} because chelating internal Ca^{2+} , by the addition of an exogenous Ca^{2+} buffer, inhibited bradykinin-induced glutamate release. Furthermore, bypassing the receptor using photolysis of caged Ca^{2+} also stimulates glutamate release[13,14,15].

In cell culture, our group had shown that astrocytic Ca^{2+} oscillations induce delayed neuronal Ca^{2+} elevations that are stimulated via glial glutamate release acting through NMDA receptors[16]. Subsequently, similar observations were made in acute brain slice preparations indicating that gliotransmission observed in culture is functional in relatively intact brain slice preparations[6,17].

Though imaging showed that astrocytes could signal to neurons, electrophysiology has been required to determine physiological roles for this pathway. Numerous laboratories demonstrated that astrocytes release glutamate and by activating neuronal receptors, these glia control synaptic transmission and neuronal excitability. Initial culture studies demonstrated that gliotransmission can modulate miniature EPSC frequency[18], as well as cause NMDA receptor-dependent slow inward currents (SICs)[19,20]. Later, these observations were confirmed in brain slice preparations[14,21,22,23,24,25, 26,27,28] and were shown to be mediated by a variety of glutamate receptors: kainate, mGluR, and

NMDA (Fig. 1)[15,29,30,31]. One difficulty associated with this type of study is to provide selective stimuli to the astrocyte in order to identify glial-evoked neuronal responses; since astrocytes are not electrically excitable, a nonelectrical stimulus is required. Photolysis has been the preferred strategy as it has been possible to provide absolute cell specificity[13,14,15,29]. Thus, in the hippocampus, photorelease of Ca^{2+} or IP_3 within a single astrocyte has been shown to cause glutamate-mediated modulation of synaptic transmission as well as neuronal excitation. Additionally, to control for potential roles of presynaptic release of glutamate, studies have shown that the inhibition of synaptic transmission does not alter gliotransmission-mediated excitation of neurons[14,22,32]. Together these studies have provided unequivocal evidence for the presence of gliotransmission in the nervous system.

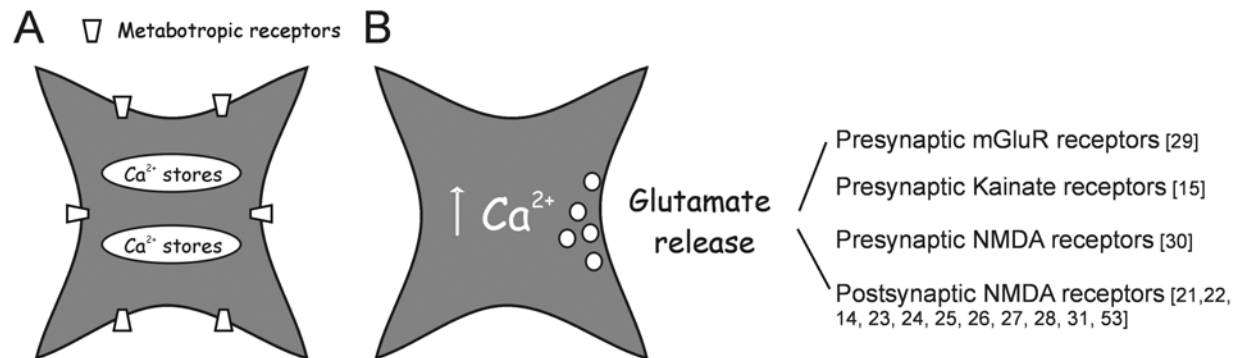


FIGURE 1. Glutamate release from astrocytes *in situ* controls neuronal excitability. (A) Astrocytes express metabotropic receptors for different neurotransmitters in the plasma membrane. Activation of these receptors triggers Ca^{2+} increases (B) within astrocytes due, mainly, to Ca^{2+} release from intracellular stores. (B) These Ca^{2+} oscillations stimulate the release of glutamate from astrocytes, which modulates neuronal excitability through the activation of a variety of different neuronal receptors.

DIFFERENTIAL Ca^{2+} CODES

Three recent studies have shown that it is inappropriate to think of astrocytic excitability simply as a Ca^{2+} elevation. Unlike the action potential that we think to be all-or-none, Ca^{2+} elevations in astrocytes come in many forms that can have differential actions. One form of transmitter release from the astrocyte is mediated through exocytosis[33]. Using total internal reflection microscopy to image fusion of vesicles with the astrocytic plasma membrane, Baljit Khakh's group has shown that two different ligands that cause Ca^{2+} elevations of similar magnitude lead to different forms of exocytosis[34]. ADP β S, which activates purinergic receptors, causes short-duration Ca^{2+} elevations (~5-sec duration) and a form of exocytosis consistent with kiss-and-run exocytosis, while thrombin, which activates PAR-1 receptor, leads to Ca^{2+} elevations of ~80-sec duration and to full-fusion exocytosis. Similarly, Chen et al. showed that different stimuli applied to astrocytes in culture can differentially cause kiss-and-run and full-fusion exocytosis[35]. What about *in situ*? A recent study from McCarthy's group strongly supports the notion that the form of Ca^{2+} elevation is essential for stimulating transmitter release[36]. They expressed a foreign receptor in astrocytes to allow selective pharmacological activation of astrocytes. Although activation of this receptor stimulated long-duration Ca^{2+} plateaus in astrocytes, neuronal actions were not detected, a result that is in disagreement with the expectations set by the work of numerous laboratories including their own[14,21,22,23,24,29]. However, when they photoreleased IP_3 , which causes transient, short-lasting Ca^{2+} increases, they were able to evoke glutamate release from the glial cell that was detected as a modulation of synaptic transmission. There are several potential explanations for this disparity, which include the possibility that the receptor is not present in the fine glial processes responsible for transmitter release. However, a more exciting possibility is that the different forms of Ca^{2+} signal evoked by these two activation pathways lead to differential effects: ligand-induced Ca^{2+} elevations

were plateau events lasting for 200–300 sec, while IP₃-induced elevations were of the order of 10–20 sec in duration. Perhaps relatively brief oscillations are required for evoking transmitter release. When taken together with the observation that some receptors, such as endothelin-1, which induces Ca²⁺ oscillations, can also inhibit exocytosis through parallel signaling pathways[37,38], it is clear we have entered into a new era where it is critical to decode the pathways activated by receptors in order to appreciate the richness of signaling possibilities within the astrocyte.

A DIVERSITY OF GLIOTRANSMITTERS

In addition to glutamate, we now know that astrocytes release additional transmitters that can have neuronal actions[39,40]. Astrocytes release ATP, which can have direct neuronal actions. Additionally, once released into the extracellular space, ectonucleotidases hydrolyse ATP to adenosine, which inhibits neurons by suppressing synaptic transmission[41] and by activating K⁺ channels[42].

Serine racemase, an enzyme that can convert L-serine to D-serine, is expressed by astrocytes and is responsible for the accumulation of D-serine within these glial cells[43]. D-serine, which is released from astrocytes, is a coagonist for the NMDA receptor binding to the so-called glycine-binding site. Selective degradation of D-serine (but not glycine) by D-amino acid oxidase (DAAO) markedly reduced the NMDA-dependent transmission in the hippocampus[44]. This result was then replicated in other brain areas[45], confirming the hypothesis that astrocytes contribute actively to NMDAR-dependent processes in the mammalian brain through the release of the gliotransmitter D-serine. Thus, astrocytes have the potential to regulate neuronal function through several transmitters. At this time, we do not know whether glutamate, D-serine, and ATP are released from the same astrocyte, or whether by analogy with neurons, there are distinct purinergic, glutamatergic, and D-serinergergic astrocytes.

GLIOTRANSMISSION IS REQUIRED FOR ADENOSINE-MEDIATED SUPPRESSION IN THE HIPPOCAMPUS

So far, we have only discussed the examples where studies have shown that astrocytes and gliotransmission are able to induce neuronal responses. Whether these pathways are required by the nervous system for brain function has been more difficult to determine. Molecular genetics has been applied to the astrocyte to inhibit purinergic gliotransmission and revealed a critical role of astrocytes in the control of extracellular adenosine[41]. The conditional expression of a dominant-negative SNARE domain (dnSNARE) selectively within astrocytes caused an enhancement of synaptic transmission within the hippocampus. It has been known for many years that there is a tonic level of extracellular adenosine in the nervous system that causes a presynaptic inhibition of synaptic transmission mediated by A1 receptors[46]. When the dnSNARE was conditionally expressed in astrocytes, this adenosine-mediated inhibition was absent[41].

In addition to demonstrating an essential role for the astrocyte in the control of synaptic transmission, these studies showed that adenosine is controlled by the astrocyte. Alcohol induces the accumulation of adenosine by inhibiting type 1 equilibrative transporters that are normally responsible for taking up extracellular adenosine[47]. Since our hippocampal studies demonstrate an important role for the gliotransmission controlling extracellular adenosine, it is tempting to speculate that astrocytes play important functions in responses to alcohol and potentially to alcohol addiction. The availability of the astrocyte-specific dnSNARE mouse should allow these studies to be performed.

mGLUR5 STIMULATES GLIAL EXCITABILITY AND GLIOTRANSMISSION IN THE NUCLEUS ACCUMBENS

Class I metabotropic receptors are known to play important roles in evoking Ca^{2+} signals in astrocytes in response to synaptic activity[5]. Additionally, one of these receptors, mGluR5, is known to play essential roles in mediating some of the actions of drugs of abuse. mGluR5 knockout mice do not exhibit cocaine self-administration behavior[48] and mGluR5 antagonists can prevent cocaine, nicotine, and morphine drug-seeking behavior[49,50,51,52]. Because of the importance of mGluR5 in mediating these behaviors and because of its importance in the activation of astrocytic Ca^{2+} signaling, we have recently performed a study on the consequences of astrocytic mGluR5 activation in the core of the nucleus accumbens, a key region for drug-seeking behavior[53].

Immunocytochemistry demonstrates that mGluR5 colocalizes with astrocytes (Fig. 2A–C) in the nucleus accumbens and that addition of an mGluR5 agonist induces astrocytic Ca^{2+} oscillations in this nucleus[53]. This raises the potential that spillover of transmitter from glutamatergic synapses could induce astrocytic signaling. Indeed, stimulation of glutamatergic afferent pathways induces astrocytic Ca^{2+} oscillations that are attenuated by the mGluR5 antagonist, MPEP (Fig. 2D,E). Because MPEP does not affect synaptic transmission at the low concentration we used (10–20 μM), these results support the idea that synaptic activity can activate astrocytic Ca^{2+} signals by engaging mGluR5 within these glial cells.

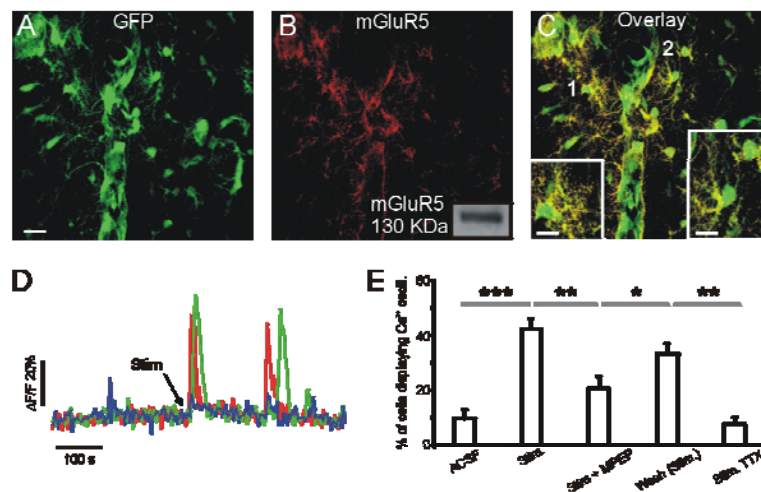


FIGURE 2. mGluR5 receptors mediate astrocyte activation following stimulation of neuronal afferents. (A–C) mGluR5 receptors (B, red) are expressed in nucleus accumbens astrocytes, identified by the expression of GFP (A, green). (D,E) Stimulation of glutamatergic afferents to the nucleus accumbens with trains of stimuli results in mGluR5-dependent activation of Ca^{2+} signaling into astrocytes. Ca^{2+} signals consist of repetitive, brief Ca^{2+} spikes. (Modified from D'Ascenzo et al.[53], copyright *Proc. Natl. Acad. Sci. U. S. A.*)

We then have asked whether astrocytic Ca^{2+} signaling leads to gliotransmission in the nucleus accumbens as has been shown elsewhere in the nervous system. Photorelease of caged Ca^{2+} within astrocytes causes SICs in medium spiny neurons (Fig. 3A–C), which are attenuated by the NMDA receptor antagonist D-AP5[53]. Moreover, synaptic activation also recruits this pathway of gliotransmission. Synaptic stimulation causes astrocyte-dependent neuronal excitation in the form of SICs that can be detected for minutes following only seconds of synaptic activity (Fig. 3D,E). Moreover, in agreement with the Ca^{2+} imaging data, this pathway requires activation of mGluR5 (Fig. 3F). Taken

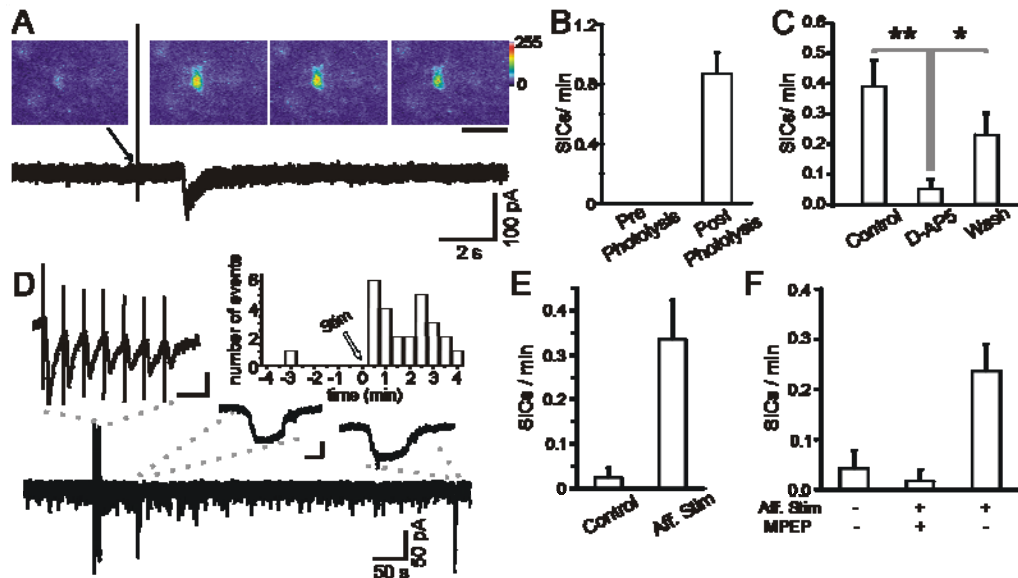


FIGURE 3. Ca^{2+} -dependent glutamate release from astrocytes generates SICs in medium spiny neurons. (A–C) Selective photolysis of astrocytic caged Ca^{2+} results in the detection of SICs in nearby nucleus accumbens neurons. (D–F) Glutamatergic afferent stimulation activates astrocytic Ca^{2+} (see Fig. 2), activates Ca^{2+} -dependent gliotransmission, and thus increases the frequency of SICs recorded in medium spiny neurons. Activation of astrocytes and, consequently, the detection of SICs are blocked by the mGluR5 antagonist MPEP (F). (Modified from D'Ascenzo et al.[53], copyright *Proc. Natl. Acad. Sci. U. S. A.*)

together, these studies show that glutamatergic synaptic activity in the nucleus accumbens leads to mGluR5-dependent release of Ca^{2+} from astrocytic IP_3 -sensitive stores, which induces the release of glutamate that then causes a feed-forward excitation of medium spiny neurons that is mediated through NMDA receptors (Fig. 4).

A particularly interesting feature of synaptic activation of astrocytes is that glial excitability is prolonged. Brief stimulation of afferents leads to oscillations that last for hundreds of seconds (Fig. 2D). Because these Ca^{2+} oscillations induce gliotransmission, which causes a feed-forward excitation of medium spiny neurons (Fig. 4), an intriguing possibility is that even relatively brief exposure to drugs of abuse will cause an mGluR5-dependent excitation of astrocytes that will cause prolonged activation of neurons.

SUMMARY AND PERSPECTIVES

Although understanding how drugs of abuse produce long-lasting neuroadaptation that underlies drug-seeking behavior and relapse is one of the fundamental issues in neuropsychology, there has been little investigation of the potential role of astrocytes in mediating these processes. However, three observations suggest that attention should be turned to these non-neuronal cells. First, Kalivas' group has shown an important role for cystine-glutamate transporters, which are thought to be glial transporters, in preventing reinstatement of drug-seeking behavior[54]. Second, mGluR5, which is essential for mediating certain behavioral responses of drugs of abuse, activates gliotransmission[53]. Finally, Bowers and Kalivas[55] showed an increase of GFAP expression in an animal model of cocaine addiction (a process termed reactive astrogliosis). This process can involve changes in gene expression and in the physiological properties of these glia cells, including Ca^{2+} excitability and gliotransmission. Given that these changes are prolonged (potentially lifelong), it will be of importance to direct experimental studies to these cells to ask whether they mediate some of the effects of drugs of abuse in the nervous system.

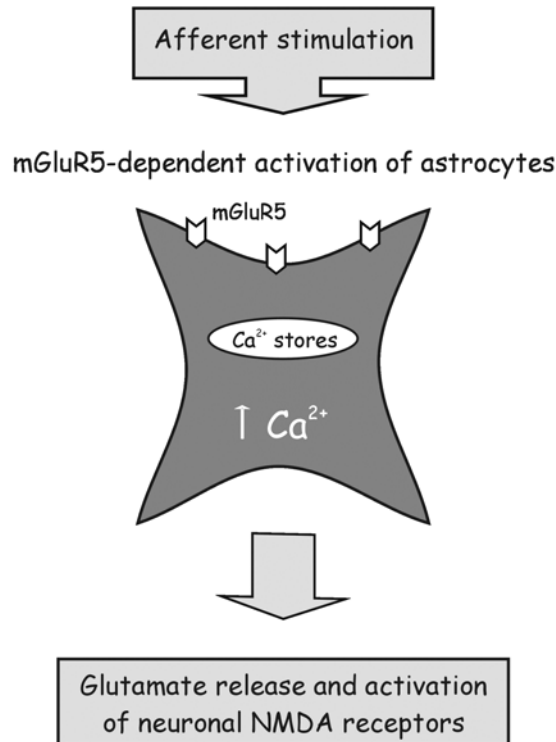


FIGURE 4. mGluR5 receptors are key regulators of gliotransmission in the nucleus accumbens. Model depicting the sequence of steps leading to Ca²⁺-dependent gliotransmission. Spillover of glutamate following glutamatergic afferent stimulation results in the activation of astrocytic mGluR5 receptors, which generate sustained Ca²⁺ oscillations into astrocytes. The oscillatory Ca²⁺ signals trigger the release of glutamate from these cells, which activates neuronal NMDA receptors.

ACKNOWLEDGMENTS

The authors' work is supported by the NINDS and NIMH.

REFERENCES

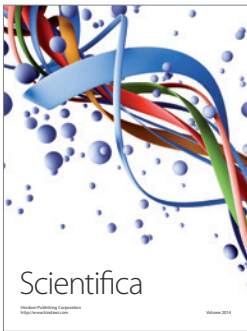
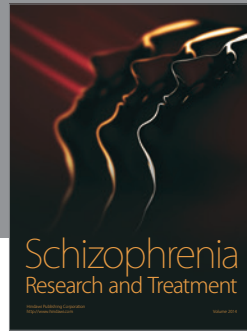
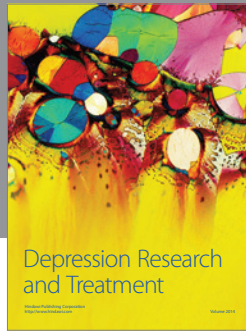
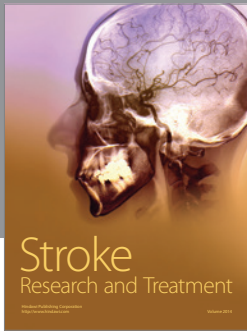
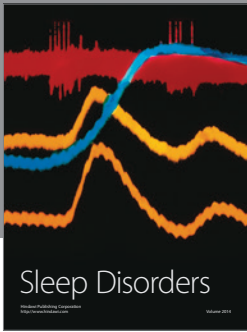
1. Volterra, A. and Meldolesi, J. (2005) Astrocytes, from brain glue to communication elements: the revolution continues. *Nat. Rev. Neurosci.* **6**, 626–640.
2. Haydon, P.G. (2001) GLIA: listening and talking to the synapse. *Nat. Rev. Neurosci.* **2**, 185–193.
3. Cornell-Bell, A.H., Finkbeiner, S.M., Cooper, M.S., and Smith, S.J. (1990) Glutamate induces calcium waves in cultured astrocytes: long-range glial signaling. *Science* **247**, 470–473.
4. Charles, A.C., Merrill, J.E., Dirksen, E.R., and Sanderson, M.J. (1991) Intercellular signaling in glial cells: calcium waves and oscillations in response to mechanical stimulation and glutamate. *Neuron* **6**, 983–992.
5. Porter, J.T. and McCarthy, K.D. (1996) Hippocampal astrocytes *in situ* respond to glutamate released from synaptic terminals. *J. Neurosci.* **16**, 5073–5081.
6. Pasti, L., Volterra, A., Pozzan, T., and Carmignoto, G. (1997) Intracellular calcium oscillations in astrocytes: a highly plastic, bidirectional form of communication between neurons and astrocytes *in situ*. *J. Neurosci.* **17**, 7817–7830.
7. Hirase, H., Qian, L., Bartho, P., and Buzsaki, G. (2004) Calcium dynamics of cortical astrocytic networks *in vivo*. *PLoS Biol.* **2**, E96.
8. Wang, X.H., Lou, N.H., Xu, Q.W., Tian, G.F., Peng, W.G., Han, X.N., Kang, J., Takano, T., and Nedergaard, M. (2006) Astrocytic Ca²⁺ signaling evoked by sensory stimulation *in vivo*. *Nat. Neurosci.* **9**, 816–823.

9. Nett, W.J., Oloff, S.H., and McCarthy, K.D. (2002) Hippocampal astrocytes in situ exhibit calcium oscillations that occur independent of neuronal activity. *J. Neurophysiol.* **87**, 528–537.
10. Aguado, F., Espinosa-Parrilla, J.F., Carmona, M.A., and Soriano, E. (2002) Neuronal activity regulates correlated network properties of spontaneous calcium transients in astrocytes in situ. *J. Neurosci.* **22**, 9430–9444.
11. Bowser, D.N. and Khakh, B.S. (2004) ATP excites interneurons and astrocytes to increase synaptic inhibition in neuronal networks. *J. Neurosci.* **24**, 8606–8620.
12. Parpura, V., Basarsky, T.A., Liu, F., Jęftinija, K., Jęftinija, S., and Haydon, P.G. (1994) Glutamate-mediated astrocyte-neuron signalling. *Nature* **369**, 744–747.
13. Parpura, V. and Haydon, P.G. (2000) Physiological astrocytic calcium levels stimulate glutamate release to modulate adjacent neurons. *Proc. Natl. Acad. Sci. U. S. A.* **97**, 8629–8634.
14. Fellin, T., Pascual, O., Gobbo, S., Pozzan, T., Haydon, P.G., and Carmignoto, G. (2004) Neuronal synchrony mediated by astrocytic glutamate through activation of extrasynaptic NMDA receptors. *Neuron* **43**, 729–743.
15. Liu, Q.S., Xu, Q., Arcuino, G., Kang, J., and Nedergaard, M. (2004) Astrocyte-mediated activation of neuronal kainate receptors. *Proc. Natl. Acad. Sci. U. S. A.* **101**, 3172–3177.
16. Araque, A., Sanzgiri, R.P., Parpura, V., and Haydon, P.G. (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.
17. Bezzi, P., Carmignoto, G., Pasti, L., Vesce, S., Rossi, D., Rizzi, B.L., Pozzan, T., and Volterra, A. (1998) Prostaglandins stimulate calcium-dependent glutamate release in astrocytes. *Nature* **391**, 281–285.
18. Araque, A., Doyle, R.T., and Haydon, P.G. (1996) Astrocytes cause slow glutamate-dependent currents and modulate the frequency of miniature synaptic currents in cultured hippocampal neurons. *Soc. Neurosci. Abstr.* 684.6.
19. Araque, A., Parpura, V., Sanzgiri, R.P., and Haydon, P.G. (1998) Glutamate-dependent astrocyte modulation of synaptic transmission between cultured hippocampal neurons. *Eur. J. Neurosci.* **10**, 2129–2142.
20. Araque, A., Li, N., Doyle, R.T., and Haydon, P.G. (2000) SNARE protein-dependent glutamate release from astrocytes. *J. Neurosci.* **20**, 666–673.
21. Parri, H.R., Gould, T.M., and Crunelli, V. (2001) Spontaneous astrocytic Ca²⁺ oscillations in situ drive NMDAR-mediated neuronal excitation. *Nat. Neurosci.* **4**, 803–812.
22. Angulo, M.C., Kozlov, A.S., Charpak, S., and Audinat, E. (2004) Glutamate released from glial cells synchronizes neuronal activity in the hippocampus. *J. Neurosci.* **24**, 6920–6927.
23. Perea, G. and Araque, A. (2005) Properties of synaptically evoked astrocyte calcium signal reveal synaptic information processing by astrocytes. *J. Neurosci.* **25**, 2192–2203.
24. Kang, N., Xu, J., Xu, Q., Nedergaard, M., and Kang, J. (2005) Astrocytic glutamate release-induced transient depolarization and epileptiform discharges in hippocampal CA1 pyramidal neurons. *J. Neurophysiol.* **94**(6), 4121–4130.
25. Tian, G.F., Azmi, H., Takano, T., Xu, Q., Peng, W., Lin, J., Oberheim, N., Lou, N., Wang, X., Zielke, H.R., Kang, J., and Nedergaard, M. (2005) An astrocytic basis of epilepsy. *Nat. Med.* **11**, 973–981.
26. Cavalier, P. and Attwell, D. (2005) Tonic release of glutamate by a DIDS-sensitive mechanism in rat hippocampal slices. *J. Physiol.* **564**, 397–410.
27. Fellin, T., Pozzan, T., and Carmignoto, G. (2006) Purinergic receptors mediate two distinct glutamate release pathways in hippocampal astrocytes. *J. Biol. Chem.* **281**, 4274–4284.
28. Kozlov, A.S., Angulo, M.C., Audinat, E., and Charpak, S. (2006) Target cell-specific modulation of neuronal activity by astrocytes. *Proc. Natl. Acad. Sci. U. S. A.* **103**, 10058–10063.
29. Fiocco, T.A. and McCarthy, K.D. (2004) Intracellular astrocyte calcium waves in situ increase the frequency of spontaneous AMPA receptor currents in CA1 pyramidal neurons. *J. Neurosci.* **24**, 722–732.
30. Jourdain, P., Bergersen, L.H., Bhaukaurally, K., Bezzi, P., Santello, M., Domercq, M., Matute, C., Tonello, F., Gundersen, V., and Volterra, A. (2007) Glutamate exocytosis from astrocytes controls synaptic strength. *Nat. Neurosci.* **10**, 331–339.
31. Lee, C.J., Mannaioni, G., Yuan, H., Woo, D.H., Gingrich, M.B., and Traynelis, S.F. (2007) Astrocytic control of synaptic NMDA receptors. *J. Physiol.* **581**, 1057–1081.
32. Pasti, L., Zonta, M., Pozzan, T., Vicini, S., and Carmignoto, G. (2001) Cytosolic calcium oscillations in astrocytes may regulate exocytotic release of glutamate. *J. Neurosci.* **21**, 477–484.
33. Bezzi, P., Gundersen, V., Galbete, J.L., Seifert, G., Steinhauser, C., Pilati, E., and Volterra, A. (2004) Astrocytes contain a vesicular compartment that is competent for regulated exocytosis of glutamate. *Nat. Neurosci.* **7**, 613–620.
34. Bowser, D.N. and Khakh, B.S. (2007) Two forms of single-vesicle astrocyte exocytosis imaged with total internal reflection fluorescence microscopy. *Proc. Natl. Acad. Sci. U. S. A.* **104**, 4212–4217.
35. Chen, X.K., Wang, L.C., Zhou, Y., Zheng, L.H., and Zhou, Z. (2005) "Kiss-and-run" glutamate secretion in cultured and freshly isolated rat hippocampal astrocytes. *J. Neurosci.* **25**, 9236–9243.
36. Fiocco, T.A., Agulhon, C., Taves, S.R., Petravic, J., Casper, K.B., Dong, X., Chen, J., and McCarthy, K.A. (2007) Selective stimulation of astrocyte calcium in situ does not affect neuronal excitatory synaptic activity. *Neuron* **54**, 611–626.
37. Andric, S.A., Zivadinovic, D., Gonzalez-Iglesias, A.E., Lachowicz, A., Tomic, M., and Stojilkovic, S.S. (2005) Endothelin-induced, long lasting, and Ca²⁺ influx-independent blockade of intrinsic secretion in pituitary cells by

- G(z) subunits. *J. Biol. Chem.* **280**, 26896–26903.
38. Grunberger, C., Obermayer, B., Klar, J., Kurtz, A., and Schweda, F. (2007) The calcium paradoxon of renin release: calcium suppresses renin exocytosis by inhibition of calcium-dependent adenylate cyclases AC5 and AC6. *Circ. Res.* **99**, 1197–1206.
 39. Halassa, M.M., Fellin, T., and Haydon, P.G. (2007) The tripartite synapse: roles for gliotransmission in health and disease. *Trends Mol. Med.* **13**, 54–63.
 40. Fellin, T., Pascual, O., and Haydon, P.G. (2006) Astrocytes coordinate synaptic networks: balanced excitation and inhibition. *Physiology* **21**, 208–215.
 41. Pascual, O., Casper, K.B., Kubera, C., Zhang, J., Revilla-Sanchez, R., Sul, J.Y., Takano, H., Moss, S.J., McCarthy, K., and Haydon, P.G. (2005) Astrocytic purinergic signaling coordinates synaptic networks. *Science* **310**, 113–116.
 42. Newman, E.A. (2003) Glial cell inhibition of neurons by release of ATP. *J. Neurosci.* **23**, 1659–1666.
 43. Martineau, M., Baux, G., and Mothet, J.P. (2006) D-serine signalling in the brain: friend and foe. *Trends Neurosci.* **29**, 481–491.
 44. Mothet, J.P., Parent, A.T., Wolosker, H., Brady, R.O., Jr., Linden, D.J., Ferris, C.D., Rogawski, M.A., and Snyder, S.H. (2000) D-Serine is an endogenous ligand for the glycine site of the N- methyl-D-aspartate receptor. *Proc. Natl. Acad. Sci. U. S. A.* **97**, 4926–4931.
 45. Panatier, A., Theodosis, D.T., Mothet, J.P., Touquet, B., Pollegioni, L., Poulain, D.A., and Oliet, S.H.R. (2006) Gliaderived D-serine controls NMDA receptor activity and synaptic memory. *Cell* **125**, 775–784.
 46. Manzoni, O.J., Manabe, T., and Nicoll, R.A. (1994) Release of adenosine by activation of NMDA receptors in the hippocampus. *Science* **265**, 2098–2101.
 47. Choi, D.S., Cascini, M.G., Mailliard, W., Young, H., Paredes, P., McMahon, T., Diamond, I., Bonci, A., and Messing, R.O. (2004) The type 1 equilibrative nucleoside transporter regulates ethanol intoxication and preference. *Nat. Neurosci.* **7**, 855–861.
 48. Chiamulera, C., Epping-Jordan, M.P., Zocchi, A., Marcon, C., Cottiny, C., Tacconi, S., Corsi, M., Orzi, F., and Conquet, F. (2001) Reinforcing and locomotor stimulant effects of cocaine are absent in mGluR5 null mutant mice. *Nat. Neurosci.* **4**, 873–874.
 49. Tessari, M., Pilla, M., Andreoli, M., Hutcheson, D.M., and Heidbreder, C.A. (2004) Antagonism at metabotropic glutamate 5 receptors inhibits nicotine- and cocaine-taking behaviours and prevents nicotine-triggered relapse to nicotine-seeking. *Eur. J. Pharmacol.* **499**, 121–133.
 50. Backstrom, P. and Hyttia, P. (2006) Ionotropic and metabotropic glutamate receptor antagonism attenuates cue-induced cocaine seeking. *Neuropsychopharmacology* **31**, 778–786.
 51. Popik, P. and Wrobel, M. (2002) Morphine conditioned reward is inhibited by MPEP, the mGluR5 antagonist. *Neuropharmacology* **43**, 1210–1217.
 52. Aoki, T., Narita, M., Shibasaki, M., and Suzuki, T. (2004) Metabotropic glutamate receptor 5 localized in the limbic forebrain is critical for the development of morphine-induced rewarding effect in mice. *Eur. J. Neurosci.* **20**, 1633–1638.
 53. D'Ascenzo, M., Fellin, T., Terunuma, M., Revilla-Sanchez, R., Meaney, D.F., Auberson, Y.P., Moss, S.J., and Haydon, P.G. (2007) mGluR5 stimulates gliotransmission in the nucleus accumbens. *Proc. Natl. Acad. Sci. U. S. A.* **104**, 1995–2000.
 54. Moran, M.M., McFarland, K., Melendez, R.I., Kalivas, P.W., and Seamans, J.K. (2005) Cystine/glutamate exchange regulates metabotropic glutamate receptor presynaptic inhibition of excitatory transmission and vulnerability to cocaine seeking. *J. Neurosci.* **25**, 6389–6393.
 55. Bowers, M.S. and Kalivas, P.W. (2003) Forebrain astroglial plasticity is induced following withdrawal from repeated cocaine administration. *Eur. J. Neurosci.* **17**, 1273–1278.

This article should be cited as follows:

Fellin, T., D'Ascenzo, M., and Haydon, P.G. (2007) Astrocytes control neuronal excitability in the nucleus accumbens. *TheScientificWorldJOURNAL* **7(S2)**, 89–97. DOI 10.1100/tsw.2007.195.



Hindawi

Submit your manuscripts at
<http://www.hindawi.com>

