Published in final edited form as:
Neuropharmacology. 2009 September ; 57(4): 343–346. doi:10.1016/j.neuropharm.2009.06.031.

Tripartite synapses: roles for astrocytic purines in the control of synaptic physiology and behavior

Michael M. Halassa[1], **Tommaso Fellin**[2], and **Philip G. Haydon**[1]

[1]Department of Neuroscience, Tufts University Schools of Medicine, Boston, MA 02111, USA

[2]Italian Institute of Technology, via Morego 30, 16163 Genova, Italy

Abstract

Astrocytes are known to release several transmitters to impact neuronal activity. Cell-specific molecular genetic attenuation of vesicular release has shown that ATP is a primary astrocytic transmitter *in situ* and *in vivo*. In this review, we discuss the biology of astrocytic ATP release highlighting the exciting discovery that lysosomes might be primary stores for the release of this gliotransmitter. In addition, we discuss the role of ATP and its metabolite adenosine on synaptic transmission and the coordination of synaptic networks. Finally, we discuss the recent elucidation of the involvement of this form of glial signaling in the modulation of mammalian behavior. By controlling neuronal A1-receptor signaling, astrocytes modulate mammalian sleep homeostasis and are essential for mediating the cognitive consequences of sleep deprivation. These discoveries begin to paint a new picture of brain function in which slow signaling glia modulate fast synaptic transmission and neuronal firing to impact behavioral output. Because these cells have privileged access to synapses, they may be valuable targets for the development of novel therapies for many neurological and psychiatric conditions.

Introduction

Astrocytes have numerous processes and are associated with tens of thousands of synapses (Bushong et al., 2002;Halassa et al., 2007b). The structural and functional association between neurons and astrocytes at the synapse prompted the coining of the term “tripartite synapse”, acknowledging the important roles of astrocyte in synaptic physiology. A recent study has now provided compelling evidence that these glial cells are vital for information processing in the brain. In this minireview we will discuss the release of ATP from astrocytes, and how this purinergic pathway modulates sleep homeostasis and cognitive impairments that follow sleep deprivation.

Astrocytes can release transmitters in a regulated manner, a process termed gliotransmission (Halassa et al., 2007a). Astrocytes contain the cellular machinery necessary for the regulated vesicular release of transmitters (Zhang et al., 2004). Molecular genetic manipulations have revealed that ATP is a major astrocytic gliotransmitter *in vivo*, and is a significant source of extracellular adenosine in the brain (Pascual et al., 2005;Serrano et al., 2006;Zhang et al., 2003). Below we review the biology of vesicular ATP release by astrocytes, its physiological significance at the synaptic level and its impact on mammalian behavior.

Regulated Release of ATP from Astrocytes

Astrocytes have been shown to release several neuroactive compounds, and they can do so by several mechanisms including transporters, hemichannels, volume-activated channels and through exocytosis (Montana et al., 2006). The process of vesicular release requires the docking and fusion of transmitter-filled vesicles with the plasma membrane, which is mediated via the formation of the SNARE complex (Hua and Scheller, 2001); a multi-protein complex that is formed by vesicular and plasma membrane proteins. SNARE proteins such as synaptobrevin II (also known as VAMP2), syntaxin and SNAP-23 have been shown to be expressed by astrocytes (Zhang et al., 2004;Montana et al., 2004;Bezzi et al., 2004). Modulatory proteins normally associated with the SNARE complex such as Munc-18 and complexin have also been shown to be expressed by these glial cells (Zhang et al., 2004). Although the debate continues regarding the size and identity of astrocytic vesicles (Bezzi et al., 2004;Zhang et al., 2004;Crippa et al., 2006), it is clear that astrocytes express the core machinery necessary for regulated exocytosis (Montana et al., 2004). Though there is substantial evidence supporting the vesicular release of glutamate, we will limit our discussion to the release of ATP as it is pertinent for specific behavioral consequences of gliotransmission that are the focus of this minireview.

The incubation of FM dyes, which label recycling vesicles, with cultured astrocytes revealed the presence of an activity-independent pool of labeled vesicles (Li et al., 2008), suggesting that these cells can continuously release vesicles regardless of exogenous stimulation, and that this recycling pool can contain lysosomes (Li et al., 2008;Zhang et al., 2007). Although primarily thought of as organelles of degradation, lysosomes of a number of cells, including melanocytes and hematopoetic cells, are known to be secretion competent (Blott and Griffiths, 2002). Astrocytic lysosomal fusion is dependent on Ca^{2+} signaling mediated by metabotropic receptors, can occur in a kiss-and-run fashion, and primarily mediates the release of ATP (Zhang et al., 2007). Astrocytic labeling with either the nucleotide dye quinicrine or the fluorescent ATP analogue Mant-ATP completely overlaps with FM-dye labeling of lysosomes in these cells. Furthermore, less than 3% of these vesicles stain positively for any of the vesicular glutamate transporters, suggesting that ATP release from astrocytes is distinct from glutamate release (Zhang et al., 2007).

Support for ATP packaging by astrocytes comes from the recent cloning and characterization of the vesicular nucleotide transporter (VNUT) (Sawada et al., 2008). This protein, previously known as SLC17A9 is primarily expressed in the brain and adrenal gland. In the brain, this protein is expressed in astrocytes (Sawada et al., 2008). Biochemical studies have shown that VNUT uses the established electrical gradient to transport ATP across the membrane, rather than actively transporting this molecule. The observation that ATP release from astrocyte is inhibited by bafilomycin (Zhang et al., 2007;Coco et al., 2003), a drug that disrupts the electrochemical gradient across intracellular organelles, provides support for the hypothesis that astrocytic ATP packaging is dependent on VNUT. In the future, it will be essential to directly test whether astrocytic lysosomes contain VNUT and whether these organelles can package ATP.

ATP and its metabolite adenosine modulate synaptic transmission

Some of the first evidence for a role for purinergic signaling by astrocytes was provided by cell culture investigations which demonstrated that astrocytes release ATP and that paracrine actions of this purine are responsible for propagating the Ca^{2+} waves that are known to develop in culture (Guthrie et al., 1999) (Bowser and Khakh, 2007). Since these initial studies released ATP has been shown to lead to several actions, either excitatory through stimulation of P2X receptors on neighboring neurons, or inhibitory through the activation of A1 receptors following the hydrolysis of ATP to adenosine

In hypothalamic slices, astrocytic release of ATP has been shown to be necessary and sufficient for synaptic potentiation induced by noradrenaline (Gordon et al., 2005). By expressing α1-adrenergic receptors, astrocytes in that brain region are able to respond to adrenergic input, and in response, release ATP onto nearby magnocellular neurosecertory neurons. Activation of P2X7 receptors on these neurons, in turn, causes an enhancement of AMPA receptor surface expression, and a resulting increase in miniature excitatory postsynaptic currents (mEPSCs). Because many noradrenergic fibers that project to the hypothalamus lack postsynaptic targets (Sawyer and Clifton, 1980), astrocytic purinergic signaling might be essential for mediating the effects of noradrenaline on hormone-related behaviors.

Studies in the mammalian retina were the first to demonstrate the importance of astrocytic purinergic signaling in suppressing neuronal activity (Newman, 2001). Using retinal wholemounts, Eric Newman has shown that light activation of photoreceptors in the retina leads to Ca^{2+} signaling in associated Muller glial cells (Newman, 2005), and as a consequence the release of ATP from these glial cells (Newman, 2003). Simultaneous voltage clamp recording of ganglion cells revealed that ATP release by Muller cells causes outward currents in these neurons. Pharmacological characterization of this phenomenon revealed that these inhibitory actions were not mediated directly by ATP, but instead by its metabolite adenosine. Activation of adenosine A1-receptor induces outward currents, while the A1-receptor antagonist DPCPX inhibits the light-induced neuronal suppression that is mediated by glia. This important finding shows that the physiological recruitment of glial cells can shape the activity of neurons.

The suppressive actions of glial adenosine have been observed in the hippocampus (Pascual et al., 2005;Serrano et al., 2006;Zhang et al., 2003). Similar to Muller cells in the retina, hippocampal astrocytes release ATP, which following its degradation by extracellular nucleotidases to adenosine, can cause a presynaptic inhibition of synaptic transmission mediated through the activation of neuronal A1-receptors. Because astrocytes express receptors and use signaling pathways that are shared with neurons it is difficult to use pharmacological manipulations to discern the role of these glia in the modulation of neuronal physiology. However, the innovative use of glia-specific toxins (Zhang et al., 2003) and selective loading of astrocytes with the Ca^{2+} chelator BAPTA (Serrano et al., 2006) have shown that inhibitory actions of adenosine on hippocampal synaptic transmission can have a glial origin. These observations point to the role of glial cells in the modulation of neuron-neuron communication, and begins to paint a very different picture of information processing in the brain than had previously been thought.

In support of the aforementioned studies using glial toxins and astrocyte-specific Ca^{2+} chelation, astrocyte-specific molecular genetic attenuation of membrane fusion shows that ATP is a primary gliotransmitter *in situ*, and that this gliotransmitter is responsible for A1-dependent neuronal suppression (Pascual et al., 2005),(Halassa et al., 2009). By overexpressing a dominant negative SNARE domain specifically and conditionally in astrocytes, it was shown that normal baseline synaptic transmission is under the control of extracellular adenosine derived from these glia. The glial specificity of this manipulation has been shown both *in vitro* and *in vivo* (Pascual et al., 2005), (Halassa et al., 2009). Evidence that this manipulation targets the vesicular pathway of transmitter release was provided by observing that SNAP-23, a plasma membrane protein involved in vesicular docking and fusion, appears in the cytoplasmic fraction when dnSNARE is expressed in astrocytes. Furthermore, this manipulation did not impair the normal physiology of the astrocyte, including K^+ buffering, neurotransmitter uptake and agonist-dependent Ca^{2+} signaling (T.F.., unpublished observations), concluding that the effect on gliotransmission is specific. This use of molecular genetics allowed for the unprecedented investigation of the role of

astrocytic purinergic signaling in synaptic physiology and mammalian behavior, two topics that we discuss below.

Astrocytes release ATP both tonically and phasically

Initial experiments using hippocampal slices derived from dnSNARE animals (animals in which dnSNARE was selectively expressed in astrocytes) showed that basal synaptic transmission was enhanced by this genetic manipulation. A sequence of studies demonstrated that enhanced synaptic transmission was due to the absence of tonic presynaptic inhibition of synaptic transmission that is mediated by neuronal A1 receptors. Bioluminescence measurements showed that astrocytic dnSNARE expression reduced extracellular ATP, which is known to be hydrolysed to adenosine by ectonucleotidases. Moreover, addition of ATP reconstituted the adenosine-dependent A1 mediated presynaptic inhibition. Thus, astrocytes continuously release ATP in a dnSNARE-sensitive and presumably vesicular manner, which is rapidly (~200 msec; (Dunwiddie et al., 1997)) degraded to adenosine to suppress synaptic transmission by activating neuronal A1-receptors. Though field potential measurements showed changes in the size of the presynaptic fiber volley and paired pulse ratio consistent with the conclusion that the effect of astrocytes is mediated through presynaptic mechanisms, one cannot rule out that postsynaptic mechanisms may also be involved in mediating the effect of astrocytic adenosine on synaptic physiology (Pascual et al., 2005, (Zhang et al., 2003).

Activation of nearby synapses (Wang et al., 2006) and neuromodulatory input (Bekar et al., 2008) can trigger astrocytic Ca^{2+} signaling. *In vivo* two-photon microscopy has shown that astrocytic Ca^{2+} signaling is triggered by physiological stimuli such as whisker (Wang et al., 2006), odorant (Petzold et al., 2008) and visual (Schummers et al., 2008) stimulation. One consequence of activity-dependent astrocytic Ca^{2+} signaling, is the modulation of vascular tone and local blood flow. Additionally, activity-dependent recruitment of astrocytes leads to a dynamic control of A1-dependent presynaptic inhibition. Tetanic stimulation of the Schaffer collaterals leads to an A1 receptor-dependent heterosynaptic depression of neighboring synapses that requires the recruitment of the astrocyte to provide the dynamic source of adenosine (Pascual et al., 2005;Serrano et al., 2006;Zhang et al., 2003). Under these elevated periods of activity additional adenosine accumlates from an astrocytic source dynamically modulate synaptic transmission. Thus as the activity of neurons waxes and wanes, the astrocyte has the potential to provide feedback signals to the network.

Astrocytic adenosine modulates sleep homeostasis and cognitive consequences of sleep loss

The activation of the A1-receptor is known to be involved in several behaviors including the regulation of sleep (Basheer et al., 2004). Sleep is known to be controlled by the circadian clock and sleep homeostat (Borbely, 1982). In contrast to the circadian regulation of sleep, a process that determines the timing of sleep as a function of environmental cues, the sleep homeostat determines the intensity of sleep as a function of prior wakefulness (Porkka-Heiskanen et al., 1997). Adenosine is thought to be specifically involved in the homeostatic regulation of sleep, because it is a chemical that accumulates as a function of prior wakefulness (Porkka-Heiskanen et al., 2000). Furthermore, introducing adenosine into the brain induces sleep (Strecker et al., 2000;Thakkar et al., 2003) and the appearance of electrophysiological markers of homeostatic sleep pressure (Benington et al., 1995) while antagonizing adenosine by pharmacological agents promotes wakefulness (Snyder et al., 1981) and attenuates the accumulation of homeostatic sleep pressure (Landolt, 2008). Genetic polymorphism in humans that promote the accumulation of brain adenosine promotes consolidated sleep and increases electrophysiological markers of homeostatic

sleep pressure (Retey et al., 2005). For many years, however, the cellular source of adenosine and its exact role in sleep regulation have been under intense investigation.

Because astrocytes are slow-signaling cells that regulate the extracellular A1-receptor tone by both a tonic and an activity-dependent manner, these cells are ideal candidates for mediating the slow progressive rise in homeostatic sleep pressure. Recent evidence showing the activity-dependence of homeostatic sleep pressure accumulation (Huber et al., 2006;Huber et al., 2004), points to the exciting possibility that activity dependent adenosine accumulation is involved in this process. The accumulation of homeostatic sleep pressure is measured by quantifying the slow wave activity (SWA) of the EEG during non rapid eye movement (NREM) sleep. SWA positively correlates with the amount of time spent in preceding wakefulness (Franken et al., 1991), and can be locally enhanced by activity-dependent processes (Huber et al., 2006;Huber et al., 2004). For example, when humans are trained on a specific visuomotor task requiring one arm, contralateral parietal cortex SWA is selectively enhanced during subsequent sleep (Huber et al., 2004). Importantly, this local increase in SWA correlated with enhanced task performance after sleep.

We studied the global brain dynamics of dnSNARE mice using EEG recordings and found that while they exhibit no change in baseline sleep timing, their baseline SWA is prominently attenuated (Halassa et al., 2009). That is, compared to wild-type animals, dnSNARE animals accumulate less SWA during their normal resting phase. Consistent with a deficit in the accumulation of homeostatic sleep pressure, these animals accumulate less SWA following a six-hour period of sleep deprivation, and show no significant increase in total sleep time following sleep deprivation. While wild-type animals show longer bouts of NREM sleep following sleep deprivation, dnSNARE animals do not. Thus, sleep pressure and its behavioral consequences are dependent on the astrocyte.

Interestingly, cognitive consequences of short-term sleep loss are also dependent on the astrocyte. Because memory consolidation of a simple learning task in mice (novel object recognition) is normally inhibited by sleep pressure accumulation, attenuating astrocytic gliotransmission protects recognition memory against the degrading effect of sleep deprivation. Importantly, electrophysiological and behavioral markers of sleep homeostasis and the cognitive consequences of sleep pressure accumulation are mimicked by a pharmacological manipulation inhibiting neuronal A1-receptors, consistent with the hypothesis that astrocytic control of adenosine mediates these behaviors.

The regulation of sleep homeostasis by astrocytes is the first demonstration that a non-neuronal cell in the brain regulates behavior. Furthermore, it provides a cellular understanding of a fundamental behavior; sleep. Because millions of people worldwide suffer from sleep disorders (De Gennaro, 2008), and many psychiatric diseases exhibit sleep abnormalities (Barthlen and Stacy, 1994), this discovery has the potential to identify new therapeutic targets for the treatment of human diseases. The selective targeting of purinergic gliotransmission may allow for fighting off sleep pressure when it is unwanted, which can be very useful for certain professions, in which prolonged wakefulness has to be coupled with high alertness. Adenosine A1-receptor agonists, or astrocyte-specific ligands that lead to the accumulation of astrocyte-derived adenosine on the other hand, may be used to inhibit the consolidation of unwanted memories, such as those formed during wars and natural disasters. This ultimately may lead to a lower incidence of post-traumatic stress disorder (PTSD).

Reference List

1. Barthlen GM, Stacy C. Dyssomnias, parasomnias, and sleep disorders associated with medical and psychiatric diseases. Mt Sinai J Med. 1994; 61:139–159. [PubMed: 8022426]

2. Basheer R, Strecker RE, Thakkar MM, McCarley RW. Adenosine and sleep-wake regulation. Prog Neurobiol. 2004; 73:379–396. [PubMed: 15313333]
3. Bekar LK, He W, Nedergaard M. Locus Coeruleus {alpha}-Adrenergic-Mediated Activation of Cortical Astrocytes In Vivo. Cereb Cortex. 2008
4. Benington JH, Kodali SK, Heller HC. Stimulation of A1 adenosine receptors mimics the electroencephalographic effects of sleep deprivation. Brain Res. 1995; 692:79–85. [PubMed: 8548323]
5. Bezzi P, Gundersen V, Galbete JL, Seifert G, Steinhauser C, Pilati E, Volterra A. Astrocytes contain a vesicular compartment that is competent for regulated exocytosis of glutamate. Nat Neurosci. 2004; 7:613–620. [PubMed: 15156145]
6. Blott EJ, Griffiths GM. Secretory lysosomes. Nat Rev Mol Cell Biol. 2002; 3:122–131. [PubMed: 11836514]
7. Borbely AA. A two process model of sleep regulation. Hum Neurobiol. 1982; 1:195–204. [PubMed: 7185792]
8. Bowser DN, Khakh BS. Vesicular ATP is the predominant cause of intercellular calcium waves in astrocytes. J Gen Physiol. 2007; 129:485–491. [PubMed: 17504911]
9. Bushong EA, Martone ME, Jones YZ, Ellisman MH. Protoplasmic astrocytes in CA1 stratum radiatum occupy separate anatomical domains. J Neurosci. 2002; 22:183–192. [PubMed: 11756501]
10. Coco S, Calegari F, Pravettoni E, Pozzi D, Taverna E, Rosa P, Matteoli M, Verderio C. Storage and release of ATP from astrocytes in culture. J Biol Chem. 2003; 278:1354–1362. [PubMed: 12414798]
11. Crippa D, Schenk U, Francolini M, Rosa P, Verderio C, Zonta M, Pozzan T, Matteoli M, Carmignoto G. Synaptobrevin2-expressing vesicles in rat astrocytes: insights into molecular characterization, dynamics and exocytosis. J Physiol. 2006; 570:567–582. [PubMed: 16322057]
12. De Gennaro L. Neurobiology wakes up for research on sleep disorders: an integration of basic and clinical research. Curr Pharm Des. 2008; 14:3384–3385. [PubMed: 19075714]
13. Dunwiddie TV, Diao L, Proctor WR. Adenine nucleotides undergo rapid, quantitative conversion to adenosine in the extracellular space in rat hippocampus. J Neurosci. 1997; 17:7673–7682. [PubMed: 9315889]
14. Franken P, Tobler I, Borbely AA. Sleep homeostasis in the rat: simulation of the time course of EEG slow-wave activity. Neurosci Lett. 1991; 130:141–144. [PubMed: 1795873]
15. Gordon GR, Baimoukhametova DV, Hewitt SA, Rajapaksha WR, Fisher TE, Bains JS. Norepinephrine triggers release of glial ATP to increase postsynaptic efficacy. Nat Neurosci. 2005; 8:1078–1086. [PubMed: 15995701]
16. Guthrie PB, Knappenberger J, Segal M, Bennett MV, Charles AC, Kater SB. ATP released from astrocytes mediates glial calcium waves. J Neurosci. 1999; 19:520–528. [PubMed: 9880572]
17. Halassa MM, Fellin T, Haydon PG. The tripartite synapse: roles for gliotransmission in health and disease. Trends Mol Med. 2007a; 13:54–63. [PubMed: 17207662]
18. Halassa MM, Fellin T, Takano H, Dong JH, Haydon PG. Synaptic islands defined by the territory of a single astrocyte. J Neurosci. 2007b; 27:6473–6477. [PubMed: 17567808]
19. Halassa MM, Florian C, Fellin T, Munoz JR, Lee SY, Abel T, Haydon PG, Frank MG. Astrocytic modulation of sleep homeostasis and cognitive consequences of sleep loss. Neuron. 2009; 61:213–219. [PubMed: 19186164]
20. Hua Y, Scheller RH. Three SNARE complexes cooperate to mediate membrane fusion. Proc Natl Acad Sci U S A. 2001; 98:8065–8070. [PubMed: 11427709]
21. Huber R, Ghilardi MF, Massimini M, Ferrarelli F, Riedner BA, Peterson MJ, Tononi G. Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. Nat Neurosci. 2006; 9:1169–1176. [PubMed: 16936722]
22. Huber R, Ghilardi MF, Massimini M, Tononi G. Local sleep and learning. Nature. 2004; 430:78–81. [PubMed: 15184907]
23. Landolt HP. Sleep homeostasis: a role for adenosine in humans? Biochem Pharmacol. 2008; 75:2070–2079. [PubMed: 18384754]

24. Li D, Ropert N, Koulakoff A, Giaume C, Oheim M. Lysosomes are the major vesicular compartment undergoing Ca2+-regulated exocytosis from cortical astrocytes. J Neurosci. 2008; 28:7648–7658. [PubMed: 18650341]
25. Montana V, Malarkey EB, Verderio C, Matteoli M, Parpura V. Vesicular transmitter release from astrocytes. Glia. 2006; 54:700–715. [PubMed: 17006898]
26. Montana V, Ni Y, Sunjara V, Hua X, Parpura V. Vesicular glutamate transporter-dependent glutamate release from astrocytes. J Neurosci. 2004; 24:2633–2642. [PubMed: 15028755]
27. Newman EA. Calcium signaling in retinal glial cells and its effect on neuronal activity. Prog Brain Res. 2001; 132:241–254. [PubMed: 11544993]
28. Newman EA. Glial cell inhibition of neurons by release of ATP. J Neurosci. 2003; 23:1659–1666. [PubMed: 12629170]
29. Newman EA. Calcium increases in retinal glial cells evoked by light-induced neuronal activity. J Neurosci. 2005; 25:5502–5510. [PubMed: 15944378]
30. Pascual O, Casper KB, Kubera C, Zhang J, Revilla-Sanchez R, Sul JY, Takano H, Moss SJ, McCarthy K, Haydon PG. Astrocytic purinergic signaling coordinates synaptic networks. Science. 2005; 310:113–116. [PubMed: 16210541]
31. Petzold GC, Albeanu DF, Sato TF, Murthy VN. Coupling of neural activity to blood flow in olfactory glomeruli is mediated by astrocytic pathways. Neuron. 2008; 58:897–910. [PubMed: 18579080]
32. Porkka-Heiskanen T, Strecker RE, McCarley RW. Brain site-specificity of extracellular adenosine concentration changes during sleep deprivation and spontaneous sleep: an in vivo microdialysis study. Neuroscience. 2000; 99:507–517. [PubMed: 11029542]
33. Porkka-Heiskanen T, Strecker RE, Thakkar M, Bjorkum AA, Greene RW, McCarley RW. Adenosine: a mediator of the sleep-inducing effects of prolonged wakefulness. Science. 1997; 276:1265–1268. [PubMed: 9157887]
34. Retey JV, Adam M, Honegger E, Khatami R, Luhmann UF, Jung HH, Berger W, Landolt HP. A functional genetic variation of adenosine deaminase affects the duration and intensity of deep sleep in humans. Proc Natl Acad Sci U S A. 2005; 102:15676–15681. [PubMed: 16221767]
35. Sawada K, Echigo N, Juge N, Miyaji T, Otsuka M, Omote H, Yamamoto A, Moriyama Y. Identification of a vesicular nucleotide transporter. Proc Natl Acad Sci U S A. 2008; 105:5683–5686. [PubMed: 18375752]
36. Sawyer CH, Clifton DK. Aminergic innervation of the hypothalamus. Fed Proc. 1980; 39:2889–2895. [PubMed: 6997091]
37. Schummers J, Yu H, Sur M. Tuned responses of astrocytes and their influence on hemodynamic signals in the visual cortex. Science. 2008; 320:1638–1643. [PubMed: 18566287]
38. Serrano A, Haddjeri N, Lacaille JC, Robitaille R. GABAergic network activation of glial cells underlies hippocampal heterosynaptic depression. J Neurosci. 2006; 26:5370–5382. [PubMed: 16707789]
39. Snyder SH, Katims JJ, Annau Z, Bruns RF, Daly JW. Adenosine receptors and behavioral actions of methylxanthines. Proc Natl Acad Sci U S A. 1981; 78:3260–3264. [PubMed: 6265942]
40. Strecker RE, Morairty S, Thakkar MM, Porkka-Heiskanen T, Basheer R, Dauphin LJ, Rainnie DG, Portas CM, Greene RW, McCarley RW. Adenosinergic modulation of basal forebrain and preoptic/anterior hypothalamic neuronal activity in the control of behavioral state. Behav Brain Res. 2000; 115:183–204. [PubMed: 11000420]
41. Thakkar MM, Delgiacco RA, Strecker RE, McCarley RW. Adenosinergic inhibition of basal forebrain wakefulness-active neurons: a simultaneous unit recording and microdialysis study in freely behaving cats. Neuroscience. 2003; 122:1107–1113. [PubMed: 14643776]
42. Wang X, Lou N, Xu Q, Tian GF, Peng WG, Han X, Kang J, Takano T, Nedergaard M. Astrocytic Ca(2+) signaling evoked by sensory stimulation in vivo. Nat Neurosci. 2006; 9:816–823. [PubMed: 16699507]
43. Zhang JM, Wang HK, Ye CQ, Ge W, Chen Y, Jiang ZL, Wu CP, Poo MM, Duan S. ATP released by astrocytes mediates glutamatergic activity-dependent heterosynaptic suppression. Neuron. 2003; 40:971–982. [PubMed: 14659095]

44. Zhang Q, Pangrsic T, Kreft M, Krzan M, Li N, Sul JY, Halassa M, Van Bockstaele E, Zorec R, Haydon PG. Fusion-related release of glutamate from astrocytes. J Biol Chem. 2004; 279:12724–12733. [PubMed: 14722063]

45. Zhang Z, Chen G, Zhou W, Song A, Xu T, Luo Q, Wang W, Gu XS, Duan S. Regulated ATP release from astrocytes through lysosome exocytosis. Nat Cell Biol. 2007; 9:945–953. [PubMed: 17618272]