profound changes in both sleep (*23*) and the sleep EEG (*24*, *25*), with a major decrease in delta activity and increase in sleep fragmentation being the hallmarks of older age in humans (*26*). These changes parallel those of *Rarb* expression (*27*) in rats, suggesting a correlated tuning of both variables. We also hypothesize that both sleepiness and slow waves in the EEG induced by dopaminergic drugs (*28*) might be explained by the close interaction between the retinoic acid receptors and the mesolimbic dopaminergic pathway (*11*).

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29. Materials and methods are available as supporting material on *Science* Online.

30. We thank B. Petit and B. Féret for technical assistance. Supported by the Swiss National Foundation for Scientific Research, the Centre National de la Recherche Scientifique (CNRS), the Institut National de la Santé et de la Recherche Médicale (INSERM), the Hôpital Universitaire de Strasbourg, the Collège de France, and the Institut Universitaire de France.

Supporting Online Material

www.sciencemag.org/cgi/content/full/310/5745/111/DC1
Materials and Methods
Figs. S1 and S2
References

19 July 2005; accepted 1 September 2005
10.1126/science.1117623

Astrocytic Purinergic Signaling Coordinates Synaptic Networks

Olivier Pascual,[1] Kristen B. Casper,[2] Cathryn Kubera,[1] Jing Zhang,[1] Raquel Revilla-Sanchez,[1] Jai-Yoon Sul,[1] Hajime Takano,[1] Stephen J. Moss,[1] Ken McCarthy,[2] Philip G. Haydon[1]*

To investigate the role of astrocytes in regulating synaptic transmission, we generated inducible transgenic mice that express a dominant-negative SNARE domain selectively in astrocytes to block the release of transmitters from these glial cells. By releasing adenosine triphosphate, which accumulates as adenosine, astrocytes tonically suppressed synaptic transmission, thereby enhancing the dynamic range for long-term potentiation and mediated activity-dependent, heterosynaptic depression. These results indicate that astrocytes are intricately linked in the regulation of synaptic strength and plasticity and provide a pathway for synaptic cross-talk.

After the discovery that neuronal transmitters evoke Ca^{2+} elevations in astrocytes (*1*, *2*), several laboratories demonstrated that astrocytes release chemical transmitters, including adenosine triphosphate (ATP) (*3*), glutamate (*4*), and D-serine (*5*). Although gliotransmitters synchronize neuronal activity (*6*) and modulate synaptic transmission (*7*–*10*), the role of gliotransmission in synaptic networks is undefined, in part because neurons and astrocytes use similar chemical transmitters and receptors. Accumulating evidence supports the idea that gliotransmitters are released through soluble *N*-ethylmaleimide–sensitive factor attachment protein receptor (SNARE) protein-dependent mechanisms (*11*–*13*). To investigate the role of gliotransmitters in synaptic networks, we generated transgenic mice in which the SNARE-dependant release of gliotransmitters was selectively impaired in astrocytes (*14*).

We expressed the cytosolic portion of the SNARE domain of synaptobrevin 2 (amino acids 1 to 96) selectively in astrocytes, a manipulation that blocks gliotransmission (*15*). We developed two lines of transgenic mice. In the first, GFAP.tTA, the astrocyte-specific glial fibrillary acidic protein (GFAP) promoter drives the expression of the "tet-Off" tetracycline transactivator (tTA). The second, tetO.SNARE, contains a tet operator (tetO)–regulated SNARE domain and lacZ and enhanced green fluorescent protein (EGFP) reporter genes (Fig. 1A). Crossing lines yields mice in which SNARE, LacZ, and EGFP transgenes are expressed in GFAP-positive astrocytes, not in neurons (Fig. 1B and E to J, and fig. S1), and in which transgene expression is suppressed by doxycycline (Dox) (Fig. 1, C and D, and fig. S1). We refer to these animals as dominant-negative SNARE (dn-SNARE) mice.

We determined if astrocyte-specific expression of the dn-SNARE domain affects synaptic transmission and plasticity by using acutely isolated hippocampal slices. The slope of Schaffer collateral–evoked field excitatory postsynaptic potentials (fEPSPs) was significantly larger ($P < 0.02$) in dn-SNARE mice expressing the transgene ($n = 10$ mice) compared to either dn-SNARE mice maintained on Dox to prevent transgene expression ($n = 9$ mice) or wild-type littermates (Fig. 2, A and B) with no change in the fiber volley (fig. S2). Thus, a SNARE-dependent process in astrocytes influences basal synaptic transmission.

To ask whether astrocytes also modulate synaptic plasticity, we studied long-term potentiation (LTP). Theta-burst stimulation applied to wild-type brain slices potentiated fEPSP slope by 232 ± 18%. The magnitude of LTP was significantly less ($P < 0.05$) in mice expressing dn-SNARE (172 ± 11%, $n = 10$ mice) (Fig. 2, C and D). Because the magnitude of LTP in wild-type mice was unaffected by maintenance on Dox, and yet this treatment prevented the change in LTP magnitude observed in dn-SNARE mice, we suggest that astrocytes control the available range for synaptic plasticity, by regulating the strength of basal synaptic transmission.

We evaluated potential roles for three gliotransmitters known to be released from astrocytes and asked whether they coordinately regulate baseline fEPSP slope and the magnitude of LTP. D-2-amino-5 phosphonopentanoate (D-AP5, 50 μM, $n = 4$ mice) to block *N*-methyl-D-aspartate (NMDA) receptors, the

[1]Department of Neuroscience, Conte Center for Integration at the Tripartite Synapse, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA. [2]Department of Pharmacology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA.

*To whom correspondence should be addressed: email: pghaydon@mail.med.upenn.edu

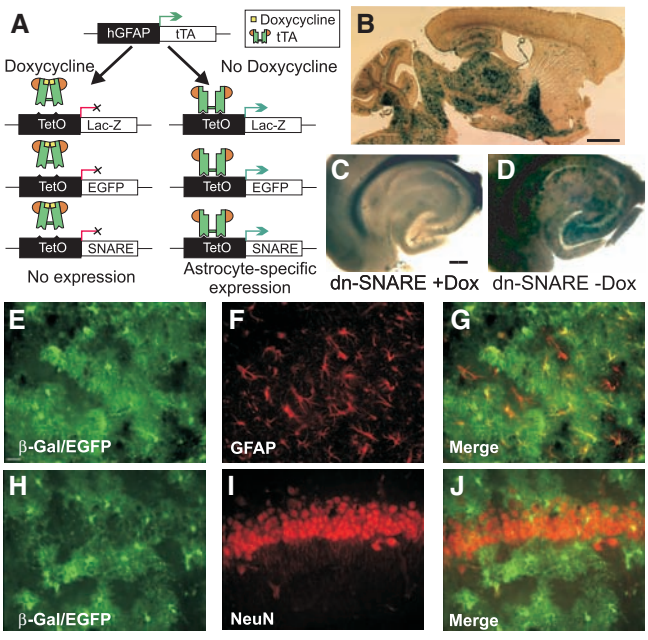

Fig. 1. Astrocyte-specific expression of the dn-SNARE domain. (**A**) Two lines of animals were generated, hGFAP.tTA and tetO.SNARE. When these lines are crossed, Dox suppresses SNARE, EGFP, and lacZ expression. (**B**) β-galactosidase (β-Gal) expression on a parasagittal section of dn-SNARE mouse brain (scale bar, 1 mm). (**C** and **D**) Slices from dn-SNARE mice (±Dox) show transgene regulation by Dox as reported by β-Gal (scale bar, 200 μm). (**E**) EGFP and β-Gal fluorescence and (**F**) GFAP immunoreactivity demonstrate expression of gene products in astrocytes. (**G**) Merged (E) and (F) images. (**H** to **J**) In hippocampal CA1, (H) EGFP and β-Gal transgenes are not expressed in neurons identified by (I) NeuN immunoreactivity. (J) Merged (H) and (I) images.

target of glial-derived D-serine and glutamate, did not change fEPSP slope (Fig. 2E) and blocked LTP (Fig. 2F). Because glial glutamate preferentially activates NR2B subunit–containing NMDA receptors (*6*), we tested ifenprodil (10 μM, $n = 9$ slices), an NR2B subunit–containing NMDA receptor antagonist, and found actions on neither the fEPSP slope (Fig. 2E) nor LTP (Fig. 2G). The P2 receptor antagonists pyridoxal-phosphate-6-azophenyl-2′,4′-disulfonic acid (PPADS) (50 μM, $n = 5$ slices) and reactive blue–2 (RB-2) (2 μM, $n = 4$ slices) had little effect on fEPSP slope (Fig. 2E), suggesting that ATP does not directly activate P2 receptors to mediate astrocytic potentiation of fEPSP and depression of LTP.

Released ATP can be converted into adenosine by ectonucleotidases (*16*). Because there is a tonic level of extracellular adenosine that acts through the A1 receptor to persistently suppress excitatory synaptic transmission (*17–20*), we asked whether adenosine mediated the effects of astrocyte-specific dn-SNARE expression. The A1 receptor antagonist

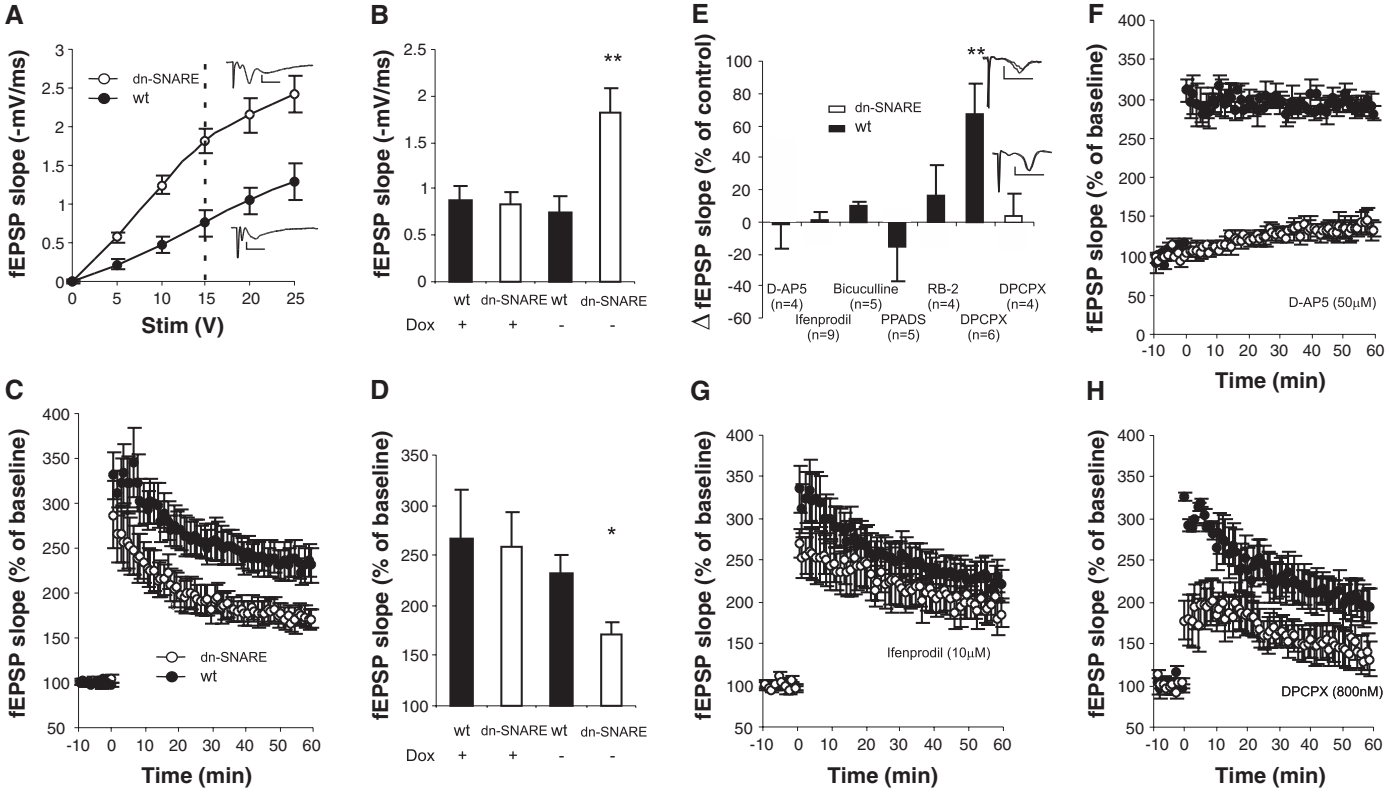

Fig. 2. Astrocytes regulate synaptic transmission and modulate plasticity through the control of extracellular adenosine. (**A** and **B**) Slope of Schaffer collateral CA1. fEPSP slope was larger in slices from dn-SNARE mice expressing this transgene (–Dox, $n = 10$ mice) compared to dn-SNARE controls (+Dox, $n = 9$ mice) and wild-type (wt) littermates (+Dox, $n = 9$ mice; –Dox, $n = 10$ mice). **, $P < 0.02$; scale bars, 1 mV, 10 ms. Stim, the dashed line represents the stimulus voltage (Stim) used to evoke the individual example traces shown as inserts. (**C** and **D**) The magnitude of theta-burst LTP was smaller when dn-SNARE was expressed in astrocytes (dn-SNARE – Dox, $n = 10$ mice; dn-SNARE + Dox, $n = 9$ mice; wt + Dox, $n = 9$ mice; and wt – Dox, $n = 10$ mice). *, $P < 0.05$. (**E**) DPCPX (800 nM) augmented the slope of the fEPSP in slices from wild-type (**, $P < 0.05$) but not dn-SNARE (–Dox) mice. (**F** to **H**) The amplitude of theta-burst LTP in slices from wild-type animals was (F) blocked by D-AP5 (50 μM, $n = 4$ slices), (G) essentially unchanged by ifenprodil (10 μM, $n = 9$ slices) and (H) reduced to an extent similar to that observed in dn-SNARE mice (–Dox) by incubation in DPCPX (800 nM, $n = 6$ mice). Data are presented as mean ± SEM.

8-cyclopentyl-1,3-dipropylxanthine (DPCPX) (800 nM) increased the fEPSP slope of wild-type slices by 67 ± 19% (n = 6 mice) (Fig. 2E) and decreased the amplitude of LTP (n = 6 slices) (Fig. 2H) to 146 ± 20%, values similar to those measured in hippocampal slices obtained from dn-SNARE mice. In contrast, DPCPX (800 nM) had no effect on baseline synaptic transmission in slices from dn-SNARE mice (3 ± 14%, n = 4 slices) (Fig. 2E). The A1 agonist 2-chloroN^6-cyclopentyladenosine (CCPA, 10 nM) reversed the actions of dn-SNARE expression by reducing the amplitude of the baseline fEPSP (n = 7 slices) (Fig. 3A) and augmenting the amplitude of LTP (n = 7 slices) (Fig. 3B).

There are two potential sources of astrocytic adenosine: loss from the cytosol through equilabrative transporters and accumulation resulting from ectonucleotidase-dependent hydrolysis of released ATP. Blockade of equilabrative nucleoside transporter 1 (ENT1) with S-(4-nitrobenzyl)-6-thioinosine (NBMPR, 100 nM), a highly selective ENT-1 antagonist (*21*), led to a further reduction in basal synaptic transmission (fig. S3), which is consistent with a role for ENT-1 in the uptake rather than the release of adenosine. We therefore studied the release of ATP from astrocytes as the potential source of adenosine accumulation, by using synaptic transmission as a sensitive assay for this nucleotide. Because P2 receptor antagonists do not change the magnitude of synaptic transmission (Fig. 2E), there is insufficient extracellular ATP under normal circumstances to activate synaptic P2 receptors. We asked whether the ectonucleotidase inhibitor ARL67156 (50 μM) would lead to an accumulation of ATP that would modulate baseline fEPSP amplitude. Superfusion of ARL67156 caused an inhibition of synaptic transmission (Fig. 3C), an action that was reversed by the P2 antagonist RB-2 (2 μM, n = 3 slices). If adenosine accumulation is mediated by the hydrolysis of ATP released from astrocytes, we would predict that the ARL67156-induced synaptic suppression would be absent in slices from dn-SNARE mice. Superfusion of ARL67156 did not significantly change (9 ± 22%) fEPSP slope in dn-SNARE slices, compared to a –56 ± 8% reduction in wild-type slices (Fig. 3C). Luciferin/luciferase imaging of extracellular ATP detected significantly less ($P < 0.05$) extracellular ATP in slices from dn-SNARE mice (12 ± 7 counts s^{-1}, n = 4 mice) compared to wild-type (26 ± 8 counts s^{-1}, n = 4 mice). These results are consistent with dn-SNARE blocking a previously described vesicular mode of ATP release from astrocytes (*22*). We then asked whether exogenous ATP would restore A1 receptor-mediated, adenosine-induced synaptic suppression. In the presence of RB-2, to block direct actions of ATP on P2 receptors, application of exogenous ATP to dn-SNARE (n = 4 slices) or wild-type (n = 4 slices) slices similarly induced a reduction in fEPSP slope that was reversed by the A1 antagonist DPCPX (Fig. 3D and fig. S4).

Tetanic stimulation of Schaffer collaterals causes an adenosine-mediated, heterosynaptic depression of neighboring unstimulated synapses (*23*). However, the source of the adenosine remains an enigma. Because stimulation of the Schaffer collaterals induces Ca^{2+} signals in astrocytes (*24*), which in turn evoke the release of gliotransmitters (*6*), and because heterosynaptic suppression has been indirectly linked to a glial-dependent mechanism (*25*), we used the dn-SNARE mice to ask whether astrocytes mediate heterosynaptic depression. Two independent pathways (S1 and S2) were each stimulated at 30-s intervals

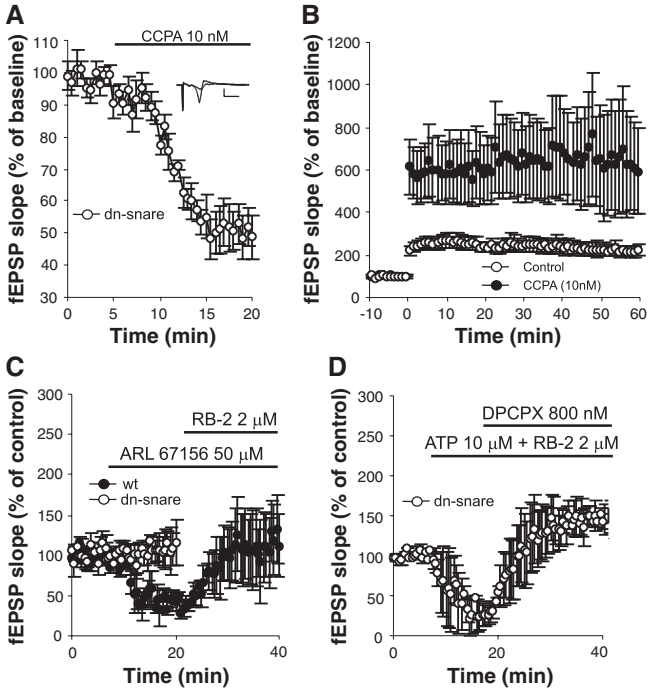

Fig. 3. dn-SNARE expression in astrocytes reduces extracellular ATP, a source of adenosine that regulates synaptic transmission. (**A** and **B**) CCPA (10 nM) reverses the effects of dn-SNARE expression by (A) reducing the fEPSP slope and (B) augmenting theta-burst–induced LTP (n = 7 slices; scale bar, 1 mV, 10 ms). (**C**) The ectonucleotidase inhibitor ARL67156 (50 μM) reduces fEPSP slope in wild-type slices (n = 3 slices), an action reversed by the P2 antagonist RB-2 (2 μM). ARL67156 does not change the fEPSP slope of dn-SNARE slices (n = 4 slices), demonstrating an absence of background ATP when dn-SNARE is expressed in astrocytes. (**D**) ATP, in the presence of RB-2 to block P2-mediated actions, reduces fEPSP slope in dn-SNARE mice (n = 4 slices), an action reversed by DPCPX (800 nM). Data are presented as mean ± SEM.

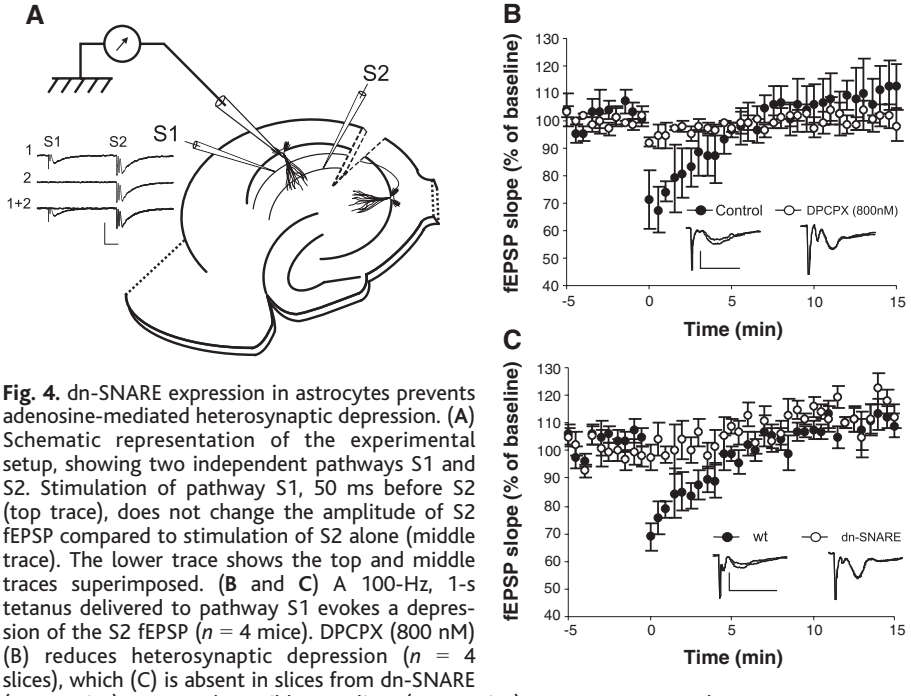

Fig. 4. dn-SNARE expression in astrocytes prevents adenosine-mediated heterosynaptic depression. (**A**) Schematic representation of the experimental setup, showing two independent pathways S1 and S2. Stimulation of pathway S1, 50 ms before S2 (top trace), does not change the amplitude of S2 fEPSP compared to stimulation of S2 alone (middle trace). The lower trace shows the top and middle traces superimposed. (**B** and **C**) A 100-Hz, 1-s tetanus delivered to pathway S1 evokes a depression of the S2 fEPSP (n = 4 mice). DPCPX (800 nM) (B) reduces heterosynaptic depression (n = 4 slices), which (C) is absent in slices from dn-SNARE (n = 5 mice) compared to wild-type slices (n = 6 mice). Data are presented as mean ± SEM.

to monitor baseline synaptic transmission (Fig. 4A). In wild-type slices, tetanic stimulation of pathway S1 (100 Hz, 1 s) evoked homosynaptic LTP together with a heterosynaptic depression of the neighboring S2 pathway. The addition of an A1 antagonist (DPCPX, 800 nM) prevented heterosynaptic depression (Fig. 4B). To control for effects of enhanced baseline transmission that result in the presence of DPCPX, we switched from normal artificial cerebrospinal fluid (ACSF) to one containing 2.4 mM Ca^{2+} and 0.6 mM Mg^{2+}, which enhanced synaptic transmission to 172 ± 8.9% (n = 3 slices) of that in control mice. We still found heterosynaptic depression to be intact (64.9 ± 8.2%, n = 3 slices) compared to ACSF controls (72.0 ± 8.6%, n = 3 slices). To determine whether astrocytes mediate adenosine-dependent depression, we repeated this study using dn-SNARE slices and found a virtual absence of heterosynaptic depression (Fig. 4C).

These studies place the astrocyte at center stage in the control of adenosine. Glial-released ATP, which is rapidly hydrolyzed to adenosine, leads to a persistent synaptic suppression mediated by A1 receptors. Because adenosine is implicated in the control of wake-to-sleep transitions (*26*, *27*) as well as responses to hypoxia, the identification of the central role of the astrocyte in regulating this nucleoside offers mechanistic insights into these processes.

The kinetics of ATP hydrolysis and adenosine accumulation provide a synaptic network with unique spatiotemporal conditions to control synaptic transmission. Fast-acting synaptic transmitters such as γ-aminobutyric acid and glutamate have high-affinity uptake systems in the vicinity of the synapse that constrain the time and distance over which a transmitter acts. Synaptic activation of an astrocyte to release ATP removes these constraints, because it takes ~200 ms before adenosine begins to accumulate (*28*). This provides time for ATP diffusion to distant sites, where it depresses synaptic transmission through accumulated adenosine, thereby providing a mechanism for cross-talk to distant synapses. In addition to activity-dependent actions, astrocytes, by persistently suppressing excitatory synaptic transmission, enhance the capability of synapses to express synaptic plasticity. Thus, the integration of synaptic activity by the astrocyte leads to a widespread coordination of synaptic networks. By suppressing excitatory transmission, astrocytes regulate the degree to which a synapse may be plastic, and during the induction of LTP, astrocyte-derived adenosine depresses neighboring unstimulated pathways.

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29. We thank I. Levitan and T. Abel for constructive criticism on versions of this manuscript, T. Abel for his constant guidance, and R. Thresher, H. Bujard, and M. Brenner for constructs used to generate transgenic vectors. Supported by funds from the National Institute of Neurological Disorders and Stroke and the National Institute of Mental Health to K.M., S.J.M., and P.G.H.

Supporting Online Material

www.sciencemag.org/cgi/content/full/310/5745/113/DC1
Materials and Methods
Figs. S1 to S4

5 July 2005; accepted 7 September 2005
10.1126/science.1116916

Failure to Detect Mismatches Between Intention and Outcome in a Simple Decision Task

Petter Johansson,[1]* Lars Hall,[1]*† Sverker Sikström,[1] Andreas Olsson[2]

A fundamental assumption of theories of decision-making is that we detect mismatches between intention and outcome, adjust our behavior in the face of error, and adapt to changing circumstances. Is this always the case? We investigated the relation between intention, choice, and introspection. Participants made choices between presented face pairs on the basis of attractiveness, while we covertly manipulated the relationship between choice and outcome that they experienced. Participants failed to notice conspicuous mismatches between their intended choice and the outcome they were presented with, while nevertheless offering introspectively derived reasons for why they chose the way they did. We call this effect choice blindness.

A fundamental assumption of theories of decision making is that intentions and outcomes form a tight loop (*1*). The ability to monitor and to compare the outcome of our choices with prior intentions and goals is seen to be critical for adaptive behavior (*2–4*). This type of cognitive control has been studied extensively, and it has been proposed that intentions work by way of forward models (*5*) that enable us to simulate the feedback from our choices and actions even before we execute them (*6*, *7*).

However, in studies of cognitive control, the intentions are often tightly specified by the task at hand (*8–10*). Although important in itself, this type of research may not tell us much about natural environments where intentions are plentiful and obscure and where the actual need for monitoring is unknown. Despite all its shortcomings, the world is in many ways a forgiving place in which to implement our decisions. Mismatches between intention and outcome are surely possible, but when we reach for a bottle of beer, we very seldomly end up with a glass of milk in our hands. But what if the world were less forgiving? What if it instead conspired to create discrepancies between the choices we make and the feedback we get? Would we always

[1]Lund University Cognitive Science, Lund University, Kungshuset Lundagård, 222 22 Lund, Sweden. [2]Department of Psychology, New York University, 6 Washington Place, New York, NY 10003, USA.

*These authors contributed equally to this work.
†To whom correspondence should be addressed. E-mail: lars.hall@lucs.lu.se