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Persistent Enhancement of Neuron–Glia Signaling Mediated by Increased Extracellular K$^+$ Accompanying Long-Term Synaptic Potentiation

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Submitted 12 February 2006; accepted in final form 9 October 2006

Ge W-P, Duan S. Persistent enhancement of neuron–glia signaling mediated by increased extracellular K$^+$ accompanying long-term synaptic potentiation. J Neurophysiol 97: 2564–2569, 2007. First published October 11, 2006; doi:10.1152/jn.00146.2006. Neuron–glia signaling is important for neural development and functions. This signaling may be regulated by neuronal activity and undergo modification similar to long-term potentiation (LTP) of neuronal synapses, a hallmark of neuronal plasticity. We found that tetanic stimulation of Schaffer collaterals (Sc) in the hippocampus that induced LTP in neurons also resulted in LTP-like persistent elevation of Sc-evoked slow depolarization in perisynaptic astrocytes. The elevated slow depolarization in astrocytes was abolished by NMDA receptor antagonist and K$^+$ channel inhibitors, but not by Ca$^{2+}$ chelator BAPTA loaded in the recorded astrocytes, suggesting involvement of an increased extracellular K$^+$ accumulation accompanying LTP of neuronal synapses. The increased K$^+$ accumulation and astrocyte depolarization after LTP induction may reduce the efficiency of glial glutamate transporters, which may contribute to the enhanced synaptic efficacy. The neuronal activity–induced persistent enhancement of neuron–glia signaling may thus have important physiological relevance.

INTRODUCTION

Astrocytes are a major type of glial cells in the brain and intimately associated with neuronal synapses (Araque et al. 2001; Grosche et al. 1999). There is increasing evidence for neuron–glia interactions mediated by secreted factors (Araque et al. 2001; Yang et al. 2003; Zhang et al. 2003). Glutamate release after neuronal activity can induce membrane depolarization and intracellular Ca$^{2+}$ elevation of perisynaptic astrocytes, which in turn can release multiple signaling molecules for immediate feedback regulation of neuronal and synaptic properties (Allen and Barres 2005; Araque et al. 2001; Zhang et al. 2003).

Long-term potentiation (LTP), a plasticity studied extensively between neuron–neuron synapses (Malenka and Nicoll 1999), was demonstrated at Schaffer collaterals (Sc)–NG2 glial cell synapses in hippocampus (Ge et al. 2006). Unlike NG2 glial cells, perisynaptic astrocytes do not receive direct synaptic inputs from neurons. Neuronal activity–induced depolarization in hippocampal astrocytes mainly consists of two components: an initial small fast component resulting from glutamate transport activity in astrocytes followed by a large slow component resulting from elevated extracellular K$^+$ ([K$^+$]o) caused by neuronal activity (Diamond et al. 1998; Luscher et al. 1998). The glutamate transporter current recorded in astrocytes has been used to monitor the level of presynaptic glutamate release before and after LTP induction in CA1 hippocampal neurons. Lack of change in the transporter current in glial cells after LTP induction, which reflects no detectable change in glutamate release from presynaptic terminals, supports the notion of postsynaptic expression of LTP (Diamond et al. 1998; Luscher et al. 1998). After LTP induction, a sustained increase in inward current in cultured Bergmann glial cells mediated by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Linden 1997) or glutamate transporter (Linden 1998) was attributed to the increased presynaptic glutamate release from granule cells. It is not clear, however, whether neuron–astrocyte signaling undergoes activity-dependent modification after tetanic Sc stimulation that induces the postsynaptic expression of LTP at synapses of Sc–CA1 pyramidal neurons (Diamond et al. 1998; Luscher et al. 1998; Nicoll 2003) and Sc–NG2 glial cells (Ge et al. 2006). In the present study, we found that, in contrast to the fast depolarization mediated by glutamate transporter activity, the slow depolarization in CA1 perisynaptic astrocytes exhibited LTP-like enhancement after high-frequency stimulation of Sc. This persistent increased astrocyte response to neuronal activity may have important physiological relevance.

METHODS

Slice preparation

Hippocampal slices were prepared as described previously (Yang et al. 2003; Zhang et al. 2003). The use and care of animals in this study follows the guideline of the Shanghai Institutes for Biological Sciences Animal Research Advisory Committee. In brief, postnatal rats (14–17 days) were anesthetized with sodium pentobarbital (50 mg/kg). After decapitation, hippocampal formation was dissected rapidly and placed in ice-cold oxygenated (95% O$_2$–5% CO$_2$) solution containing (in mM): 119 NaCl, 2.5 KCl, 2.5 CaCl$_2$, 1.3 MgSO$_4$, 1 NaH$_2$PO$_4$, 26.2 NaHCO$_3$, and 11 glucose. Transverse slices (400 μm, thick) were cut with a vibratome (Campden Instruments, Loughborough, UK) and maintained in an incubation chamber for 2 h at 37°C before recording. During experiments, a single slice was transferred to a submersion recording chamber and was continuously perfused with the above-mentioned oxygenated solution (3.0 ml/min) at room temperature (22–25°C). Slices were visualized with infrared optics using an Olympus microscope (BX50WI) equipped with differential interference contrast (DIC) optics.

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Electrophysiology

Whole cell patch-clamp recordings were made from astrocytes in *s. radiatum* in the presence of γ-aminobutyric acid type A (GABA<sub>A</sub>) antagonist picrotoxin (100 μM). Recording pipettes were routinely filled with a solution containing (in mM): 125 K-gluconate, 15 KCl, 10 HEPES, 8 NaCl, 3 Na<sub>2</sub>ATP, 0.3 Na-GTP, 10 Na<sub>2</sub>-phosphocreatine, and 0.2 EGTA (290–300 mOsm, pH 7.3 adjusted with KOH). For experiments to inhibit potassium channels, the pipette solution contained (in mM): 125 Cs-glutamate, 5 CsCl, 10 HEPES, 3 Na<sub>2</sub>ATP, 0.3 Na-GTP, 0.2 EGTA, 10 Na<sub>2</sub>-phosphocreatine, 10 tetraethylammonium (TEA)-Cl, and 2 BaCl<sub>2</sub> (290–300 mOsm, pH 7.3 adjusted with CsOH). In addition, 1 mM CsCl (to inhibit potassium channel more efficiently) and 0.3 μM 6,7-dinitroquinoxaline-2,3-dione (DNQX; to suppress potential epileptic activity induced by K<sup>+</sup> channel inhibition) were added to the bath for K<sup>+</sup> channel inhibition experiments. Membrane potential of the astrocyte was held at −80 mV. Constant current pulses (10–40 μA, 100 μs, 0.05 or 0.033 Hz) were applied through concentric bipolar electrodes (MCE-100, RMI) placed at Sc of *s. radiatum* in the CA1 region to induce glial responses or field excitatory postsynaptic potential (fEPSP). Field EPSPs were recorded from the dentrites of CA1 pyramidal cells using a glass electrode filled with 3 M NaCl (2–3 MΩ) or normal artificial cerebrospinal fluid (ACSF, 10–20 MΩ). The diameter of the glass electrode tip for field potential recordings was <1 μm. The stimulus intensity was set to generate a fEPSP with amplitude roughly 30–40% of the maximum response. The same extracellular electrode was also used to apply tetic stimulations to induce LTP or persistent enhancement of glial responses. Tetanic stimulation consists of 100-ms pulses applied at 10 Hz for 1 s, with the same intensity as the test stimulus for evoking fEPSPs. The amplitude of slow inward currents or depolarization in astrocytes induced by Sc stimulation was obtained by calculating the mean amplitude during a 50-ms time window starting at 500 ms after the stimulus artifact. Membrane resistance was monitored by measuring the amplitude of the hyperpolarization induced by current injections (−100 pA, 100 ms) through the recording pipette at an interval of 20 s. Spontaneous EPSCs (sEPSCs) in neurons were recorded under a gap-free mode.

Data were accepted for analysis only when astrocyte responses and the input resistance did not vary >15% of the average values during the control period. Signals filtered at 5 kHz using the amplifier circuitry were sampled at 10 kHz and analyzed with Clampex 8.2 (Axon Instruments). Spontaneous EPSCs were analyzed using Mini-analysis program (Synaptosoft). Data are presented as means ± SE and statistical differences were determined by Student’s t-test. Reagents were obtained from Sigma–Aldrich (St. Louis, MO) except where noted.

Immunostaining

Glia cells were filled with 0.1% biocytin (ε-N-biotinyl-l-lysine) or 0.2% Lucifer yellow dissolved in the recording pipette solution. Only one cell was injected with biocytin in each slice. Slices were fixed with 4% paraformaldehyde at room temperature for 3 h before treatment with 0.2% Triton X-100 for 30 min and blocking solution containing 10% bovine serum albumin for 1 h. Slices were then stained with anti–glial fibrillary acidic protein (GFAP) antibody (1:1,000, polyclonal, Chemicon, Temecula, CA) for 48 h at 4°C. Biocytin was visualized with FITC-conjugated streptavidin or Texas-Red streptavidin (1:1,000, Vector Laboratories) after washing to remove excess primary antibodies. The slice was imaged with an Olympus confocal microscope (Fluoview 500 IX71) using a ×60, 1.2 NA water-immersion objective.

Results

Whole cell recordings were made from astrocytes in *s. radiatum* of the CA1 region (Fig. 1A). Astrocytes were identiﬁed by their low input resistance (11.2 ± 0.4 MΩ, n = 154), the absence of action potential recorded under current clamping (Fig. 1D), and the linear current–voltage relationship without apparent transient A-type K<sup>+</sup> current and Na<sup>+</sup> current recorded under voltage clamping (Fig. 1E). Postrecording immunostaining for astrocyte-specific marker GFAP showed positive staining...
itive staining in all (15/15) cells that exhibited the above properties. Furthermore, biocytin or Lucifer yellow loaded into the recorded astrocyte was found to spread to many surrounding cells (Fig. 1B), consistent with the existence of extensive coupling among astrocytes through gap junctions.

Stimulation of Sc evoked inward current in astrocytes (Fig. 1F). As reported previously (Bergles and Jahr 1997; Diamond et al. 1998; Luscher et al. 1998), two distinct components of the inward current could be discerned: The slow inward current (Fig. 1F, arrowhead) lasted for >10 s and was largely abolished when K+ channels were inhibited by loading the astrocyte with a solution containing TEA, Ba2+, and Cs+ through the recording pipette, together with Cs+ (1 mM) added to the extracellular medium. A low concentration of DNQX (0.3 μM), an antagonist of non-N-methyl-d-aspartate receptors (NMDARs), was also added to the extracellular solution to prevent possible epileptic activity induced by extracellular Cs+ (D’Ambrosio et al. 1998; Zhou and Kimelberg 2000). We found that such a low concentration of extracellular Cs+ and DNQX, although evoking a small depolarization in neuron (29.4 ± 6.4 pA, n = 6), did not induce a significant change in either frequency of sEPSC or firing pattern of CA1 pyramidal neurons (Supplemental Fig. 1).1 The fast inward current (duration, 90.1 ± 11.3 ms, n = 8) unmasked in the presence of K+ channel inhibitors (Fig. 1G) was produced by activity of glutamate transporters in the recorded astrocyte (Bergles and Jahr 1997; Diamond et al. 1998; Luscher et al. 1998), as confirmed by application of glutamate transporter inhibitor α,α′-threo-benzoyloxyaspartate (TBOA, 100 μM) that caused >80% (85.4 ± 2.2%, n = 7) inhibition of the fast inward current (Fig. 1H). The slow inward current was also significantly inhibited by kynurenic acid (Kyn, 1 mM) (66.3 ± 4.7%, at 500 ms, n = 6; Fig. 1, F and G), a broad-spectrum blocker of ionotropic glutamate receptors, suggesting that this slow inward current was caused by [K+]i accumulation associated with glutamate receptor activation (Bergles and Jahr 1997; Diamond et al. 1998; Luscher et al. 1998). We noted that glutamate transporter current revealed by treatment with K+ channel inhibitors with or without Kyn (54.4 ± 7.4 pA, n = 10) was significant larger than that revealed by treatment with Kyn alone (20.3 ± 2.0 pA, n = 4) (compare Fig. 1F with 1G). This increased transport current may be caused not by increased presynaptic glutamate release, but by the decreased current shunting resulting from increased membrane resistance arising from K+ channel blockage because such treatment did not induce significant changes in either the frequency or the amplitude of sEPSC (Supplemental Fig. 1, C and D).

Field potentials were recorded in the CA1 area to monitor neuronal LTP, together with whole cell patch-clamp recording of nearby astrocytes in current-clamp mode (Fig. 2A), in the presence of the GABA_A antagonist picrotoxin. We found that tetanic stimulation (100 Hz, 1 s) of Sc consistently induced LTP of Sc–CA1 pyramidal cell synapses (Fig. 2, B and C). The amplitude of the fiber volley, which reflects the presynaptic firing (Sims and Hartell 2005), was not changed significantly after LTP induction (98.4 ± 1.9%, n = 14, Supplemental Fig. 2), consistent with the postsynaptic expression of LTP in this brain region. Interestingly, a sustained increase in the amplitude of the slow depolarization in astrocytes was observed soon after the tetanic stimulation (Figs. 2, D and E and 3F). Consistent with previous studies (Bliss and Collingridge 1993), induction of LTP in CA1 neurons was abolished by NMDAR antagonist D,L-2-amino-5-phosphonovaleric acid (APV, 100 μM; Fig. 3, D and F). Furthermore, the enhancement of slow depolarization in astrocytes was also abolished by APV (Fig. 3, A and F).

Intracellular Ca2+ elevation is critical for LTP induction at neuronal synapses (Bliss and Collingridge 1993; Malenka and Nicoll 1999). However, abolishing intracellular Ca2+ elevation in astrocytes by loading fast Ca2+ chelator BAPTA (10 mM) through the recording pipette had no effect on the enhancement of slow depolarization in astrocytes (Fig. 3, B and F). In some cells, even with higher loads of BAPTA (40 mM), the persistent enhancement of slow depolarization still existed (161.4 ± 36.3%, n = 3). Inhibition of K+ channels by the treatment described above significantly reduced the Sc-induced slow depolarization in astrocytes. Furthermore, Sc tetanic stimulations did not enhance the residual slow depolarization observed in the astrocyte under the above treatment (Fig. 3, C and F), whereas the neuronal LTP was still induced. Moreover, the late phase (20 min after tetanic stimulation) of neuronal LTP was more robust in the presence of K+ channel inhibitor (Fig. 3F), possibly as a result of the enhanced Ca2+ influx after tetanic

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1 The online version of this article contains supplemental data.
stimulation arising from inhibition of K⁺ channel–mediated membrane repolarization. Consistent with previous reports (Diamond et al. 1998; Luscher et al. 1998), the amplitude of the transporter activity-induced fast depolarization in astrocytes, unmasked by inhibition of K⁺ channels (Fig. 1G), did not change significantly after tetanus stimulation of Sc (Fig. 3F). Taken together, these results strongly support the notion that the potentiation of Sc-evoked astrocyte responses reflects an elevated accumulation of [K⁺]₀ associated with the enhanced neuronal synaptic response after LTP induction.

The membrane potential of astrocytes is sensitive to the change in [K⁺]₀. To estimate the extent of [K⁺]₀ elevation induced by Sc stimulation, we examined the membrane potential changes in astrocytes induced by perfusion of extracellular solutions with different concentrations of [K⁺]. We found that changing [K⁺]₀ from 2.5 mM (control) to 3, 5, and 10 mM induced averaged depolarization of 3.4 ± 0.4 (n = 6), 12.0 ± 0.8 (n = 5), and 24.5 ± 0.4 mV (n = 4), respectively, estimated from an averaged resting membrane potential of −87.26 mV (Fig. 4, A and B). A logarithmic relation between [K⁺]₀ and astrocyte membrane potential can be established based on the equation: Y = −103.22 + 40.42 × lg X, where Y refers to membrane potential and X refers to [K⁺]₀.

The slow inward current (slow depolarization) recorded in the astrocyte reflects an increase in [K⁺]₀ caused by Sc stimulation-induced neuronal activity. Consistent with this notion, Sc-induced slow inward current in astrocytes was largely abolished by treatment with K⁺ channel inhibitors (Fig. 1G). The result that Kyn also largely blocked the slow inward current (Fig. 1, F and G; see also Luscher et al. 1998) suggests that [K⁺]₀ elevation inducing the slow inward current/depolarization in astrocytes is mainly caused by activation of glutamate receptors after Sc stimulation.

Treatment of glutamate in cultured astrocytes induced an increased expression of glial glutamate transporter GLAST (Duan et al. 1999). Furthermore, glutamate transporter activity in Purkinje cells undergoes activity-dependent plasticity after LTP induction at cerebellar climbing fiber–Purkinje cell synapses (Shen and Linden 2005). However, Sc-tetanic stimulation failed to induce a change in the fast depolarizing responses in hippocampal astrocytes mediated by glial transport activity (Fig. 3F; see also Diamond et al. 1998; Luscher et al. 1998). Lack of change in the transporter current in glial cells after LTP induction has been taken as evidence for the postsynaptic

FIG. 3. Mechanisms underlying the persistent enhancement of astrocyte response induced by tetanic Sc stimulation. Both persistent enhancement of astrocyte slow depolarization (A) and LTP of neuronal fEPSP (D) induced by tetanic Sc stimulation were abolished by perfusion with N-methyl-D-aspartate receptor antagonist d,l-2-amino-5-phosphonovaleric acid (APV, 100 μM). B: intracellular loading BAPTA (10 mM) in astrocytes did not inhibit the persistent enhancement of astrocyte slow depolarization. C: persistent enhancement of astrocyte slow depolarization was significantly inhibited by K⁺ channel blockers (see METHODS). E: application of Cs⁺ extracellularly as in C did not inhibit neuronal LTP. Data shown in A–E are averaged and normalized as in Fig. 2. C and E. Arrows indicate the time when tetanic Sc stimulation was applied. F: summary of percentage changes in the amplitude of fEPSP (‘neuron–fEPSP’) or astrocyte responses (‘astrocyte’) induced by tetanic Sc stimulation under control (Ctrl) or various treatments. Averaged data from Sc-induced responses during 20–40 min after tetanic Sc stimulation as shown in A–E were compared with those before tetanic stimulation for each recording. Amplitude of the fast depolarization mediated by glutamate transporter activity (Transporter) was measured in the presence of K⁺ channel inhibitors, as indicated by the asterisk (*) in Fig. 1G. Numbers associated with each column indicates number of cells in each group, * indicates significant change of the response after tetanic Sc stimulation (P < 0.01).

FIG. 4. Astrocyte depolarization induced by elevated extracellular K⁺ ([K⁺]₀). A: example traces from an astrocyte in response to different [K⁺]₀ values from a control level of 2.5 mM [K⁺]₀. B: summary of data as shown in A. Number associated with each column indicates number of cells recorded in each group. C: plot of astrocyte membrane potentials with different values of [K⁺]₀ (log₁₀ scale) based on data shown in B with an averaged membrane potential of −87.26 mV under the control [K⁺]₀ level (2.5 mM). Data are best fitted (line) with the equation Y = −103.22 + 40.42 × lg X, where Y is the membrane potential and X is [K⁺]₀.
expression of LTP (Diamond et al. 1998; Luscher et al. 1998). In the latter studies the AMPA receptor was blocked to isolate the glutamate transporter current in glial cells, a procedure that would prevent K⁺ accumulation caused by glutamate receptor activation (Fig. 1F), thus masking the increased glial response after LTP induction. On the other hand, a sustained increase in the glial fast inward current mediated by activation of AMPA receptors (Linden 1997) or glutamate transporter (Linden 1998) in glial cells has been attributed to the increased presynaptic glutamate release after LTP induction in cerebellar neurons. Our results showed that after the induction of CA1 hippocampal LTP, which is expressed postsynaptically (Diamond et al. 1998; Ge et al. 2006; Luscher et al. 1998; Nicoll 2003), the Sc-evoked slow depolarization in astrocytes was also increased, as a result of increased K⁺ accumulation arising from potentiated neuronal synaptic transmission. This conclusion is supported by results that the potentiated astrocyte response persisted in astrocytes loaded with Ca²⁺ chelator BAPTA, but was blocked either by treatment with K⁺ channel inhibitors or by application of APV, an antagonist of NMDA receptors that prevented neuronal LTP (Fig. 3). Thus astrocytes may passively respond to neuronal LTP expressed either pre- or postsynaptically. The “passive” property of sustained potentiation of depolarization in persynaptic astrocytes after neuronal LTP induction is in contrast to that of the potentiation of Sc-induced EPSC in NG2 glial cells, where the Ca²⁺-permeable AMPA receptors at the persynaptic NG2 glial cells play critical roles in both induction and expression of the “glial LTP” (Ge et al. 2006).

As a result of the abundant expression of inward rectifying K⁺ channels, the membrane potential of astrocytes faithfully reflects K⁺ equilibrating potential and is very sensitive to the change of [K⁺]o (Orkand et al. 1966; Zhou and Kimelberg 2000). By measuring the amplitudes of astrocyte depolarizations in response to perfusion of different concentrations of [K⁺]o, we were able to obtain a logarithmic relation between [K⁺]o and astrocyte membrane potential (Fig. 4C). Because of current shunting by extensive gap-junction coupling and low membrane resistance (resulting from abundant expression of K⁺ channels) in astrocytes, the amplitude of depolarization induced at remote astrocyte processes near synapses will always be substantially underestimated by whole cell recording at astrocyte soma. Accordingly, the actual [K⁺]o elevation at the localized synaptic region induced by synaptic activity after LTP induction will be even much higher than we estimated. Glutamate transporters expressed in persynaptic astrocytes are critical for clearing glutamate in the synaptic cleft and thus play a key role in controlling the strength and kinetics of synaptic activity (Bergles and Jahr 1997; Oliet et al. 2001). The efficiency of glial glutamate transporter will be reduced after LTP induction because of the decreased driving force for the transporter (Swanson and Duan 1999) caused by the increased K⁺ accumulation and membrane depolarization. Reduction of glutamate clearance in the synaptic cleft will further enhance synaptic efficacy, although it is not clear how much the decreased efficiency of glial glutamate transporter contributes to the enhanced synaptic activity after LTP induction. Synaptic activity induces the release of signaling molecules from astrocytes, which in turn modulate neuronal activities (Fellin et al. 2005; Paucal et al. 2005; Zhang et al. 2003). In addition, astrocytes play a critical role in neuronal LTP induction by secreting d-serine (Yang et al. 2003), a coagonist of NMDA receptors found only in astrocytes (Mothe et al. 2000). After LTP induction, neuronal activity may cause an increased depolarization and [Ca²⁺]i elevation in astrocytes, leading to enhanced release of signaling molecules from astrocytes and thus enhanced feedback modulation of the function and plasticity of neuronal synapses. Although the enhanced astrocyte depolarization after LTP induction reflects the “passive” response of astrocytes to increased synaptic activity, it may affect both the expression and the extent of neuronal LTP.

In summary, the activity-dependent plasticity of neuron–glia signaling reported here underscores the dynamics of neuron–glia interaction. The functions of neural circuits are intimately tied to that of glial cells embedding the circuits. Glial cells are now recognized to serve not only for long-term trophic support of neurons, but also for immediate feedback regulation of neuronal and synaptic properties (Araque et al. 2001; Fellin et al. 2005; Zhang et al. 2003). Our finding that neuron-evoked rapid glial responses undergo activity-induced changes immediately suggests the existence of plasticity in the feedback regulation of neural circuits by glial cells.

ACKNOWLEDGMENTS

We thank M.-M. Poo for critical comments on the manuscript and H.-K. Wang, J.-B. Mao, and Z.-J. Zhang for technical assistance.

GRANTS

This work was supported by Major State Basic Research Program of China Grant G200077800 and National Natural Science Foundation of China Grant 30321002.

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