RESEARCH

Differential Expression of Short-term Potentiation by AMPA and NMDA Receptors in Dentate Gyrus

Xiaping Xie,¹ German Barrionuevo,² and Theodore W. Berger^{1,3}

¹Department of Biomedical Engineering and Program in Neuroscience
University of Southern California
Los Angeles, California 90089

²Department of Neuroscience and
Center for the Neural Basis of Cognition
University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Abstract

Both α -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) and *N*-methyl-D-aspartate (NMDA) glutamatergic receptor subtypes in hippocampus have been shown to express long-term potentiation (LTP), a form of synaptic modification believed to be involved in memory formation. Because of their postsynaptic localization, any differential expression of LTP by the two receptor subtypes would strongly support the existence of a postsynaptic mechanism of LTP expression. In this study, electrophysiological recordings from dentate granule cells were used to compare the potentiation of AMPA and NMDA receptor-mediated responses occurring during the initial phase of LTP, typically identified as STP. Results revealed that high-frequency stimulation (HFS) of perforant path afferents induces a robust STP of both AMPA and NMDA receptor-mediated components of granule cell EPSPs (referred to as AMPA STP and NMDA STP, respectively). Although STP for both receptor subtypes decayed to an asymptotic, steady-state level of LTP and could be induced repetitively, there were substantial differences in several aspects of AMPA and NMDA STP dynamics. STP of the AMPA receptor reached its peak magnitude ~30 sec after HFS and decayed with a time constant of ~6 min. In contrast, peak

magnitude of NMDA STP always appeared immediately after HFS and decayed with a time constant of only 1 min. Single-pulse stimulation of perforant path afferents paired with postsynaptic depolarization also induced LTP of both AMPA and NMDA components. When this induction paradigm was used, however, only the AMPA component showed significant STP. Our results demonstrate that AMPA and NMDA receptors exhibit markedly different degrees of activity-dependent, short-term modifiability, with the possibility that STP of the NMDA receptor reflects primarily post-tetanic potentiation (PTP). In addition, our results strongly suggest that the mechanisms underlying STP of the AMPA receptor are postsynaptic in origin.

Introduction

Hippocampal glutamatergic synapses have long been known to express robust long-term potentiation (LTP), a long-lasting form of activity-dependent synaptic plasticity. Extensive studies during the last two decades have established several hypotheses concerning the cellular-molecular mechanisms underlying the induction and expression of LTP. For hippocampal synapses at which *N*-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) glutamatergic receptors coexist, it is now established that the NMDA receptor subtype plays a critical role in the induction process: Excitatory synaptic input must depolarize the postsynaptic neuron to an extent that there is substantial unblocking of NMDA receptor channels (Mayer

³Corresponding author.

1984; Nowak et al. 1984; Mayer and Westbrook 1987). There is less agreement with respect to the mechanisms underlying LTP expression, though one of the more widely considered hypotheses is that the maintained expression of LTP reflects a modification of AMPA receptor channels and thus, is postsynaptic in origin (Lynch and Baudry 1984; Maren et al. 1993; Tocco et al. 1994). This hypothesis is supported by the observation that, following the induction of LTP and subsequent pharmacological blockade of AMPA receptors, the residual NMDA receptor-mediated component of synaptic responses shows only a small magnitude of potentiation compared with that exhibited by the AMPA receptor-mediated component. This finding is consistent with the supposition that NMDA receptor binding in the synapse is near saturation during each release of transmitter as a result of the high affinity of the receptor for glutamate (Herron et al. 1986; Harris and Cotman 1986; Friedlander et al. 1990; Grover and Teyler 1990; Zalutsky and Nicoll 1990). More recently, however, the view that LTP expression is mediated exclusively by changes in AMPA receptors has been challenged by us and other who have demonstrated that the NMDA component can express LTP with a magnitude equivalent to that expressed by the AMPA component (Xie et al. 1992a,b; O'Connor et al. 1995). However, no conclusive evidence has allowed resolution of the issue of whether or not AMPA LTP and NMDA LTP share a common synaptic expression mechanism.

The maintenance of LTP has been identified as including three stages (Bliss and Collingridge 1993; Reymann 1993). An initial, decremental stage is referred to as short-term potentiation (STP), and is characterized by a near-immediate increase in response magnitude followed by a rapid decay of potentiation to an asymptotic, steady-state level. STP typically has been reported to have a time course of 10 min or less, though durations as long as 90 min have been suggested (Larson and Lynch 1988; Anwyl et al. 1989; Gustafsson et al. 1989; Malenka 1991; Colino et al. 1992; Hanse and Gustafsson 1992; Malenka et al. 1992). As noted above, many previous studies have focused on the relative magnitudes of LTP expressed by AMPA and NMDA receptor subtypes, and results have been sufficiently varied so as to provide support for either a pre- or postsynaptic expression mechanism. In contrast, few studies have attempted to compare the dynamics of STP expressed by AMPA and NMDA receptor subtypes.

A presynaptic mechanism of expression should result in STP dynamics that are similar for NMDA and AMPA receptor-mediated EPSPs, whereas a difference in dynamics would provide strong evidence that STP of at least one of the two receptor subtypes reflects a postsynaptic modification.

In the studies reported here, we show that STP of both AMPA and NMDA receptor-mediated responses occurred immediately after high-frequency stimulation (HFS), rapidly decayed to an asymptotic, steady-state level, and be induced repetitively. However, the onset and decay time course of STP differed markedly for AMPA and NMDA receptor-mediated EPSPs. Furthermore, we found that STP induction of AMPA and NMDA receptor-mediated responses exhibited a different frequency dependence. Finally, we examined the interaction between STP and LTP in an attempt to understand the mechanisms that might underlie the expression of STP. We also demonstrate that STP was unlikely to be caused by the direct action of calcium on the AMPA receptor/channel.

Materials and Methods

Hippocampal slices were prepared from male New Zealand white rabbits. Animals first were anesthetized with 5% halothane, and the skull overlying the parietal cortex was removed bilaterally. The hippocampal formation and overlying neocortex from each hemisphere were extracted and gently separated. Both hippocampi were sectioned into blocks while being washed with cold, oxygenated medium, and slices of tissue (500 μ m thick) then were put perpendicular to the longitudinal axis using a vibratome. Slices were superfused with medium consisting of (in mM): 126 NaCl, 5 KCl, 1.25 NaH_2PO_4 , 26 NaHCO_3 , 10 glucose, 2 CaCl_2 , and 0.1 or 1.0 MgSO_4 , aerated with 95% O_2 /5% CO_2 , and maintained at 32°C.

Perforant path input to dentate granule cells was activated using a bipolar nichrome stimulating electrode placed in the medial third of the stratum moleculare. Baseline synaptic responses were evoked at a frequency of either 0.10 Hz or 0.05 Hz with a 0.1 msec duration pulses (intensity 20–150 μ A, chosen for any one experiment so as to evoke 50–60% of the maximum control response). HFS of perforant path fibers was used to induce STP and LTP, and consisted of four trains of pulses with each train composed of 10 pulses delivered with a frequency of 100 Hz; a 5 sec intertrain interval was used. HFS was applied at the same stimulus inten-

DIFFERENTIAL EXPRESSION OF AMPA AND NMDA STP

sity used to evoke baseline responses. In some experiments, LTP was induced using 6–10 single pulses (0.1 Hz) paired with brief postsynaptic depolarization (Gustafsson et al. 1987). The postsynaptic depolarization (to -40 mV) was produced by injecting 0.1 – 0.3 nA current through the intracellular recording electrode. The current injection started 10 msec before each single pulse and was continued for 100 msec. EPSPs and EPSCs were recorded intracellularly from granule cells using sharp or whole cell microelectrodes, respectively. Sharp electrodes (glass 1BBL, 1.0 mm OD, WPI) were filled with 2 M KMeSO_4 (resistance: 100 – 150 M Ω). Whole cell electrodes (glass 7052, 1.65 mm OD, Garner) were filled with (in mM): 120 cesium gluconate, 5 KCl, 2 MgSO_4 , 10 N -2-hydroxy-ethyl-piperazine- N -2-ethanesulfonic acid (HEPES), 0.1 CaCl_2 , 1.0 BAPTA, and 3.0 ATP-Mg (resistance: 6 – 9 M Ω). The solution was buffered to pH 6.8 and the final osmolarity was 270 mmole/kg. The mean resting membrane potential for all cells included in the present analysis was 62.0 ± 0.2 mV, and the mean input resistance was 198 ± 10 M Ω ($n = 18$). Field EPSPs were recorded in the stratum moleculare of the dentate gyrus using microelectrodes (glass thin wall 1.5 mm OD, WPI) filled with 2.0 M NaCl (resistance: 1 – 2 M Ω).

When field EPSPs and whole cell EPSCs were recorded simultaneously, the extracellular recording electrode was placed in the medial third of the stratum moleculare, 200 μm from the whole cell pipette. Data acquisition and analysis were completed using an AxoBasic system. Data from different slices were combined by normalizing amplitudes or onset slopes of the EPSPs and EPSCs and were compared using standard parametric statistical techniques.

CNQX (6-cyano-7-nitroquinaxaline-2,3-dione, Tocris Neuramin), D-APV (D-2-amino-5-phosphonovaleate, Cambridge Research Biochemicals), and 25 μM picrotoxin (Sigma) were applied via the perfusion bath. Picrotoxin was present in media during all experiments.

Results

DIFFERENTIAL DYNAMICS OF AMPA AND NMDA STP

AMPA AND NMDA STP EXHIBIT DIFFERENT TIME COURSES

The first experiments examined the possibility of a differential expression of STP by AMPA and

Figure 1: NMDA STP decays faster than AMPA STP. (A) I-V curve of NMDA receptor-mediated EPSC at 0.1 mM Mg^{2+} ($n = 4$). (B) STP and LTP expressed by NMDA-mediated field EPSPs ($n = 7$). (C) Field EPSPs were recorded before (black traces) and after (gray traces) D-APV (50 μM) at 0.1 mM Mg^{2+} (upper) and 1.0 mM Mg^{2+} (lower). (D) STP and LTP expressed by AMPA-mediated field EPSPs ($n = 8$). Note that the amount of LTP in the later phase is similar for these two groups. Data shown in A and B were collected in presence of the AMPA receptor antagonist CNQX (10 μM).

NMDA receptors. NMDA receptor-mediated field EPSPs were isolated pharmacologically by blocking AMPA receptors with the specific antagonist, CNQX (10 μ M) and the magnitude of the NMDA response was enhanced by reducing $[Mg^{2+}]_o$ to 0.1 mM. In reduced $[Mg^{2+}]_o$, a negative slope conductance was clearly present in the I–V curve (Fig. 1A), indicating that properties of the receptor-channel remained characteristic of higher concentrations of $[Mg^{2+}]_o$ (Nowak et al. 1984). Under these conditions, HFS induced both STP and LTP of NMDA receptor-mediated field EPSPs (Fig. 1B). When the decay time course of STP was fitted with a single exponential curve, the averaged decay time constant for NMDA STP was found to be 1.2 ± 0.20 min ($n = 8$).

When slices were perfused with media covering 1.0 mM Mg^{2+} , field EPSPs recorded in response to 0.1 Hz synaptic activation were almost exclusively AMPA receptor-mediated (Fig. 1C). HFS induced both STP and LTP of the AMPA response (Fig. 1D, open circles), though the decay time constant of AMPA STP (6.39 ± 0.86 min, $n = 12$) was found to be substantially longer than that for NMDA receptor-mediated EPSPs ($F = 12.14$, $P < 0.01$). The difference in STP decay time constants for AMPA and NMDA responses was not due to the differences in $[Mg^{2+}]_o$. When AMPA STP was examined in 0.1 mM $[Mg^{2+}]_o$, the averaged decay time constant was 6.30 ± 0.86 min ($n = 11$) (Fig. 1D, solid circles), virtually identical to that observed in the presence of 1.0 mM $[Mg^{2+}]_o$ ($P > 0.1$). STP of the AMPA and NMDA receptor channels also differed with respect to the time to maximum expression. The peak magnitude of potentiation for the NMDA component was observed immediately following HFS, that is, in response to the first post-HFS control stimulation (within 5 sec), while the peak magnitude of STP for the AMPA component appeared ~ 30 sec after HFS (cf. Fig. 1B and C).

DISSOCIATION OF AMPA STP AND NMDA STP

The above experiments revealed that STP expressed by NMDA receptors decays with a significantly shorter time course than the STP expressed by AMPA receptors. The decay rate for NMDA STP is sufficiently rapid that it overlaps substantially with that typically observed for PTP (Magleby et al. 1987). As a consequence, we evaluated the possibility that the HFS-induced enhancement of the NMDA receptor-mediated response reflects prima-

rily the presynaptic mechanisms responsible for PTP. It has been demonstrated that stimulation of presynaptic afferents with single pulses paired with postsynaptic depolarization is sufficient to induce AMPA STP and LTP (Gustafsson et al. 1987), without an associated induction of PTP. We used a similar protocol (10 pulses at 0.1 Hz each paired with postsynaptic depolarization) in an attempt to dissociate NMDA STP and PTP. Results showed LTP was induced for both glutamatergic receptor subtypes (AMPA LTP, $n = 6$; NMDA LTP, $n = 6$). However, AMPA LTP always was preceded by a marked STP (Fig. 2B), whereas NMDA LTP was not (Fig. 2A). Considering the rapid decay of NMDA STP observed in response to HFS, it was possible that NMDA STP was being induced by pairing of single-pulse stimulation and postsynaptic depolarization, but the STP decayed before the conditioning protocol was completed. Therefore, a test stimulation was applied between each conditioning pair to monitor the development of potentiation. Only a gradual, progressive increase in the amplitude of NMDA receptor-mediated EPSPs was observed. These findings demonstrate that coacti-

Figure 2: The induction of NMDA STP, but not AMPA STP, requires HFS. Intracellular EPSPs were recorded. (A) In presence of CNQX (10 μ M), single-stimulation pulses of perforant path fibers paired with intracellular postsynaptic depolarization induced NMDA LTP without STP. HFS then induced STP superimposed on the previously induced LTP. (B) In absence of CNQX, single-pulse stimulation of the perforant path paired with intracellular depolarization induced both AMPA STP and LTP, similar to that observed in response to HFS.

DIFFERENTIAL EXPRESSION OF AMPA AND NMDA STP

vation of pre- and postsynaptic elements is required for the induction of AMPA and NMDA LTP, as well as for the induction of AMPA STP, but not for NMDA STP. Thus, the LTP-inducing protocol that did not elicit PTP also failed to induce NMDA STP, suggesting that a substantial component of what initially was identified as NMDA STP actually may reflect PTP.

EXPRESSION MECHANISM OF STP

STP CAN BE REPETITIVELY INDUCED AFTER SATURATION OF LTP

Results of the experiments described above indicate that STP and LTP share common mechanisms of induction. If STP and LTP also reflect the same mechanisms of expression, then inducing the maximum level of LTP should occlude STP. Alternatively, if the mechanism of STP expression is independent of the mechanism of LTP expression, then repetitive administration of HFS should lead to different levels of maximum potentiation. Specifically, the total potentiation induced by a second HFS should be greater than that induced by the first HFS, because the total potentiation observed immediately after the second HFS would represent the sum of STP and LTP, whereas the potentiation observed immediately after the first HFS would represent only STP (or STP and the partial development of LTP). To test for the possibility of occlusion between STP and LTP, three

sets of HFSs were applied at 30-min intervals. Figure 3A and B show results for the AMPA and NMDA receptor-mediated components, respectively. The first HFS resulted in both STP and LTP. The second and additional HFSs induced only STP, which was expressed with a constant magnitude, superimposed on a stable and maximal level of LTP.

In another series of experiments, we found that if slices first were incubated in 0 mM Mg^{2+} for 30 min, HFS resulted only in STP and could no longer induce LTP (Fig. 3C). After the first HFS in 0 mM Mg , 1.0 mM Mg^{2+} was added to the perfusing medium. The second HFS then was applied and again failed to induce LTP, though did result in STP. One possible explanation for this result is that the condition of 0 Mg^{2+} , through some unknown mechanism, leads to a disabling of the LTP induction mechanism (Coan et al. 1989). An alternative interpretation is that in 0 mM Mg^{2+} spontaneous release of neurotransmitter is increased to an extent that basal levels of excitation are sufficient to induce maximum levels of LTP. Based on the latter interpretation, the finding of a selective induction of STP is consistent with the result of repetitive administration of HFS, that is, saturation of LTP does not completely occlude STP.

EXPRESSION OF AMPA STP IS PARTIALLY OCCLUDED BY LTP

The results of repeated HFS might have failed to reveal independent expression of STP and LTP

Figure 3: STP is not prevented by saturation of LTP. Field EPSPs were recorded. (A) Repetitive induction of AMPA STP in the absence of CNQX ($n=6$). (B) Repetitive induction of NMDA STP in the presence of 10 μ M CNQX ($n=5$). In both cases, the first HFS produced saturating levels of LTP. Two additional HFSs delivered at an interval of 30 min induced STP again without any additional increase in LTP. (C). In the absence of both $[Mg^{2+}]_o$ and CNQX, HFS induced only STP; when perfusion with 1.0 mM Mg^{2+} was resumed, HFS still induced only STP ($n=5$).

because the superimposed levels of STP and LTP reached a maximum possible postsynaptic response, in which case additional STP would not be detectable even if its expression is independent of LTP. To test this possibility, we examined the effect of prior induction of LTP on submaximal levels of STP. As shown in Figure 4, a 10 Hz HFS first was applied, which induced a moderate STP ($154.2 \pm 12.9\%$, $n = 4$; see 1 vs. 2 in Fig. 4) and a small magnitude of LTP. A 100-Hz HFS then was applied, which resulted in the induction of a larger magnitude of STP and a robust LTP. When the STP induced by the 100-Hz HFS decayed and a stable level of LTP was achieved, a second 10 Hz HFS was applied. Based on the logic outlined above, if the expression mechanisms of STP and LTP are independent, then the magnitude of STP induced by the second 10 Hz HFS should be equivalent to that induced by the first 10 Hz HFS superimposed on the baseline represented by the asymptotic level of LTP. This was not observed, however. Instead, a smaller magnitude STP was induced by the second 10-Hz HFS ($120.2 \pm 3.3\%$; see 3 vs. 4 in Fig. 4), indicating partial occlusion, that is, AMPA STP and LTP expression are not entirely independent of one another.

STP IS NOT DUE TO A DIRECT EFFECT OF Ca^{2+} ON THE RECEPTOR CHANNEL

The results presented in the previous sections strongly support the possibility that the mechanism of expression for AMPA STP is postsynaptic in origin. One speculation is that the STP may be caused by the direct effect of increased $[\text{Ca}^{2+}]_i$ on the postsynaptic membrane-bound AMPA receptor channel during and immediately after HFS. If this is the case, then intracellular dialysis, which normally occurs with a prolonged whole cell re-

cording configuration, should not prevent the repetitive induction of STP, because dialysis should reduce only intracellular soluble proteins but not the existing number of glutamatergic receptors in the postsynaptic membrane. Field EPSPs and whole cell EPSCs were monitored from the same slices. Two sets of HFS were applied to the perforant path axons at intervals of 20–30 min (voltage clamped cells were depolarized to -20 mV during HFS). STP and LTP were observed in 15 of 18 cells after the first HFS. Among the 15 cells, however, only one cell showed moderate STP following the second HFS, while all simultaneously recorded field EPSPs revealed robust STP and LTP following both sets of HFS. Figure 5 shows representative waveforms and averaged results from the 15 cells. Our explanation for the failure to observe STP with the second HFS is that the cell was thoroughly dialyzed during the 20–30 min following the first HFS. This result makes it unlikely that STP is due to a direct Ca^{2+} effect on the intracellular membrane.

Discussion

In this series of experiments, we identified several fundamental differences between the STP expressed by AMPA and NMDA subtypes of glutamatergic receptors. First, STP of AMPA receptors has a longer time course for both its development and decay than the STP expressed by NMDA receptors. In addition, the induction of AMPA STP does not require high-frequency synaptic activation, whereas NMDA STP does. These differences strongly suggest that AMPA STP is expressed postsynaptically. A presynaptic, PTP-like phenomenon also may contribute to AMPA STP, but because of its brevity, it may not account for a significant portion of AMPA STP profile (Asztely et al. 1992). In contrast, the very rapid onset, short de-

Figure 4: Partial occlusion of STP by LTP. Field EPSPs were recorded. First, 10 Hz HFS was applied that induced STP and a small magnitude LTP. Then, 100 Hz HFS was delivered, which resulted in both STP and LTP, each of which was of greater magnitude than that induced by the 10 Hz HFS. When the decay of STP was complete, a second 10 Hz HFS was given. The magnitude of STP induced by the second 10 Hz HFS was markedly reduced compared with that induced by the first 10 Hz HFS, indicating partial occlusion by the LTP induced by the 100 Hz HFS.

Figure 5: Dialysis prevents STP induction. Two sets of HFS were applied at an interval of 20–30 min. STP was observed in both whole cell EPSCs and field EPSPs following the first HFS. STP was seen only in the field EPSP following the second HFS.

cay time, and frequency-dependent induction characteristics of NMDA STP also are common to PTP, raising the possibility that the initial potentiation expressed by the NMDA component is composed primarily of PTP. The results of experiments using single-pulse stimulation of presynaptic afferents paired with intracellular depolarization support this interpretation, and indicate that the relative magnitudes of STP expressed by AMPA and NMDA receptors also clearly can differ substantially. In fact, without further experiments, we cannot rule out the possibility that the NMDA receptor does not express STP, but only PTP and LTP.

Pharmacologically isolating NMDA components allowed us to measure directly the peak amplitude of EPSPs mediated by the NMDA receptor channel. Other authors (Asztely et al. 1992; Clark and Collingridge 1995) have used the late decay phase of the complex EPSP to estimate the dynamics of NMDA STP, and the onset slope of the same EPSP to estimate the dynamics for AMPA STP. Using this less direct method, the STP time constants for the AMPA and NMDA components have been determined to be similar ($\tau \sim 5$ min). The validity of estimating the AMPA and NMDA components using the complex EPSP was based in part on the finding that, in control conditions, amplitude of the late component of the EPSP (50–100 msec after stimulation) was not affected by CNQX (Asztely et al. 1992) and that it demonstrated an I–V curve typical for the NMDA channel (Clark and Collingridge 1995). The assumption of independence of the two components is less likely during potenti-

ation, however. Potentiation of the early AMPA component could easily contaminate the late NMDA component. In addition, potentiation of the late component would likely increase the sensitivity of the NMDA response to AMPA receptor-induced depolarization. Interestingly, Clark and Collingridge (1995) noted that the decay time constant of NMDA STP also was ~ 1 min when peak amplitude of the NMDA receptor was measured after being isolated pharmacologically.

There are currently two different views concerning the relation between STP and LTP expression. One view holds that LTP is the consolidation of the same underlying mechanism of expression of STP. From this assumption, it follows that STP represents a “weak induction of LTP,” such that LTP has a variable duration and/or stability determined by the induction conditions (Gustafsson et al. 1989; Malenka 1991). The alternative view is that the mechanisms of expression of STP and LTP are separate and independent (Davies et al. 1989; Hanse and Gustafsson 1992; Bliss and Collingridge 1993; Colley and Routtenberg 1993; Stevens 1993). In support of the first view, it has been found that stimulation parameters causing weak postsynaptic depolarization, such as the 10-Hz HFS protocol used in the present study, induce mainly STP, whereas stimulation parameters leading to strong postsynaptic depolarization, such as the 100 Hz HFS protocol used here, stabilize the temporarily potentiated synaptic strength of STP, resulting in LTP (Gustafsson et al. 1989; Malenka 1991; Hanse and Gustafsson 1994). The partial occlusion of STP by LTP observed in our experiments also is consistent with the hypothesis that LTP represents a consolidation of the same mechanism underlying expression of STP. However, our results also showed that regardless of the stimulation parameters used, the magnitude of STP is always greater than that of LTP. This was observed for saturating levels of both forms of potentiation; that is, even when LTP reached clearly nondecremental levels, additional HFS still could induce STP repeatedly. It is difficult to reconcile these results with the view of STP as a “weak induction of LTP.”

STP is distinguished from persistent forms of potentiation by its relatively short duration, being on the order of 10–15 min rather than the hours or days characteristic of LTP (Bliss and Collingridge 1993; Reymann 1993). The decay time constant of AMPA STP in the present study was ~ 6 min with a total duration of 10–15 min. Based on

Xie et al.

this estimate of time course, the STP investigated in the present experiments is the same phenomenon described and studied previously by others using experimental conditions that do not involve pharmacological blockage of second messenger kinase systems (Larson and Lynch 1988; Anwyl et al. 1989; Gustafsson et al. 1989; Henry and Segal 1990; Malenka 1991; Colino et al. 1992; Hanse and Gustafsson 1992). Several second messenger kinases contribute to NMDA receptor-dependent LTP (Bliss and Collingridge 1993; Reymann 1993). Among them, Ca^{2+} -calmodulin (CaM)-dependent processes have been considered to be responsible for STP expression. However, the blocking effect of calmidazolium on STP has not been confirmed by others using different CaM inhibitors (Malenka et al. 1989; Malinow et al. 1989; Haley et al. 1992; Smith et al. 1993) or using CaM kinase II mutant mice (Silva et al. 1992). These results have led some to propose the existence of a second messenger-independent STP, in which case, increased postsynaptic Ca^{2+} may have a direct effect on the AMPA receptor. However, our results (see Fig. 5) do not support this hypothesis. In fact, inhibition of different second messenger kinases, including CAM (Malenka et al. 1989; Malinow et al. 1989; Smith et al. 1993), PKC (Reymann et al. 1988; Wang and Feng 1992; Cheng et al. 1994), cAMP-dependent protein kinase, and tyrosine kinase (O'Dell et al. 1991), reduce the magnitude of STP without abolishing it completely. Thus, an additional possibility is that the expression of STP results from the activation of one or more of those second messenger systems, with the consequence that STP cannot be completely eliminated blocking only one kinase system.

Acknowledgments

This work was supported by the Office of Naval Research (N00014-94-1-0568), the National Institute of Mental Health (MH00343 and MH51722), and the Human Frontiers Science Organization.

The publication costs of this article were defrayed in part by payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 USC section 1734 solely to indicate this fact.

References

- Anwyl, R., D. Mulkeen, and M.J. Rowan. 1989. The role of N-methyl-D-aspartate receptors in the generation of short-term potentiation in the rat hippocampus. *Brain Res.* **503**: 148–151.
- Asztely, F., H. Wigström, and B. Gustafsson. 1992. The

relative contribution of NMDA receptor channels in the expression of long-term potentiation in the hippocampal CA1 region. *Eur. J. Neurosci.* **4**: 681–690.

Bliss, T.V.P. and G.L. Collingridge. 1993. A synaptic model of memory—Long-term potentiation in the hippocampus. *Nature* **361**: 31–39.

Cheng, G., X.W. Rong, and T.P. Feng. 1994. Block of induction and maintenance of calcium-induced LTP by inhibition of protein-kinase-C in postsynaptic neuron in hippocampal CA1 region. *Brain Res.* **646**: 230–234.

Clark, K.A. and G.L. Collingridge. 1995. Synaptic potentiation of dual-component excitatory postsynaptic currents in the rat hippocampus. *J. Physiol.* **482**: 39–52.

Coan, E.J., A.J. Irving, and G.L. Collingridge. 1989. Low-frequency activation of the NMDA receptor system can prevent the induction of LTP. *Neurosci. Lett.* **105**: 205–210.

Colley, P.A. and A. Routtenberg. 1993. Long-term potentiation as synaptic dialogue. *Brain Res. Rev.* **18**: 115–122.

Colino, A., Y.-Y. Huang, and R.C. Malenka. 1992. Characterization of the integration time for the stabilization of long-term potentiation in area CA1 of the hippocampus. *J. Neurosci.* **12**: 180–187.

Davies, S.N., R.A.J. Lester, K.G. Reymann, and G.L. Collingridge. 1989. Temporally distinct pre- and post-synaptic mechanisms maintain long-term potentiation. *Natur* **338**: 500–503.

Friedlander, M.J., R.J. Sayer, and S.J. Redman. 1990. Evaluation of long-term potentiation of small compound and unitary EPSPs at the hippocampal CA3-CA1 synapse. *J. Neurosci.* **10**: 814–825.

Grover, L.M. and T.J. Teyler. 1990. Two components of long-term potentiation induced by different patterns of afferent activation. *Nature* **347**: 477–479.

Gustafsson, B., H. Wigström, W.C. Abraham, and Y.-Y. Huang. 1987. Long-term potentiation in the hippocampus using depolarizing current pulses as the conditioning stimulus to single volley synaptic potentials. *J. Neurosci.* **7**: 774–780.

Gustafsson, B., F. Asztely, E. Hanse, and H. Wigström. 1989. Onset characteristics of long-term potentiation in the guinea-pig hippocampal CA1 region in vitro. *Eur. J. Neurosci.* **1**: 382–394.

Haley, J.E., G.L. Wilcox, and P.F. Chapman. 1992. The role of nitric oxide in hippocampal long-term potentiation. *Neuron* **8**: 211–216.

Hanse, E. and B. Gustafsson. 1992. Postsynaptic, but not presynaptic, activity controls the early time course of long-term potentiation in the dentate gyrus. *J. Neurosci.* **12**: 3226–3240.

DIFFERENTIAL EXPRESSION OF AMPA AND NMDA STP

- . 1994. Staurosporine impairs both short-term and long-term potentiation in the dentate gyrus *in vitro*. *Neurosci.* **58**: 263–274.
- Harris, E.W. and C.W. Cotman. 1986. Long-term potentiation of guinea pig mossy fiber responses is not blocked by *N*-methyl-D-aspartate antagonists. *Neurosci. Lett.* **70**: 132–137.
- Henry, M. and M. Segal. 1990. Acetylcholine potentiates responses to *N*-methyl-D-aspartate in the rat hippocampus. *Neurosci. Lett.* **113**: 62–65.
- Herron, C.E., R.A.J. Lester, E.J. Coan, and G.L. Collingridge. 1986. Frequency-dependent involvement of NMDA receptors in the hippocampus: A novel synaptic mechanism. *Nature* **322**: 265–268.
- Larson, J. and G. Lynch. 1988. Role of *N*-methyl-D-aspartate receptors in the induction of synaptic potentiation by burst stimulation patterned after the hippocampal q-rhythm. *Brain Res.* **441**: 111–118.
- Lynch, G. and M. Baudry. 1984. The biochemistry of memory: A new and specific hypothesis. *Science* **224**: 1057–1063.
- Magleby, K.L. 1987. Short-term changes in synaptic efficacy. In *Synaptic function* (ed. G.M. Edelman, W.E. Gall, and W.M. Cowan), pp. 21–56. John Wiley and Sons, New York, NY.
- Malenka, R.C. 1991. Postsynaptic factors control the duration of synaptic enhancement in area CA1 of the hippocampus. *Neuron* **6**: 53–60.
- Malenka, R.C., J.A. Kauer, D.J. Perkel, M.D. Mauk, P.T. Kelly, R.A. Nicoll, and M.N. Waxham. 1989. An essential role for postsynaptic calmodulin and protein kinase activity in long-term potentiation. *Nature* **340**: 554–557.
- Malenka, R.A., B. Lancaster, and R.S. Zucker. 1992. Temporal limits on the rise in postsynaptic calcium required for the induction of long-term potentiation. *Neuron* **9**: 121–128.
- Malinow, R., H. Schulman, and R.W. Tsien. 1989. Inhibition of postsynaptic PKC or CaMKII blocks induction but not expression of LTP. *Science* **245**: 862–866.
- Maren, S., G. Tocco, S. Standley, M. Baudry, and R.F. Thompson. 1993. Postsynaptic factors in the expression of long-term potentiation (LTP): Increased glutamate receptor binding following LTP induction *in vivo*. *Proc. Natl. Acad. Sci.* **90**: 9654–9658.
- Mayer, M.L. and G. Westbrook. 1987. Permeation and block of *N*-methyl-D-aspartic acid receptor channels by divalent cations in mouse cultured central neurones. *J. Physiol.* **394**: 501–527.
- Mayer, M.L., G.L. Westbrook, and P.B. Guthrie. 1984. Voltage-dependent block by Mg^{2+} of NMDA responses in spinal cord neurones. *Nature* **309**: 261–263.
- Nowak, L., P. Bregestovski, and P. Ascher. 1984. Magnesium gates glutamate-activated channels in mouse central neurones. *Nature* **307**: 462–465.
- O'Connor, J.J., M.J. Rowan, and R. Anwyl. 1995. Tetanically induced LTP involves a similar increase in the AMPA and NMDA receptor components of the excitatory postsynaptic current: Investigations of the involvement of mGlu receptors. *J. Neurosci.* **15**: 2013–2020.
- O'Dell, T.J., E.R. Kandel, and S.G.N. Grant. 1991. Long-term potentiation in the hippocampus is blocked by tyrosine kinase inhibitors. *Nature* **353**: 558–560.
- Reymann, K.G. 1993. Mechanisms underlying synaptic long-term potentiation in the hippocampus: Focus on postsynaptic glutamate receptors and protein kinases. *Funct. Neurol. (Suppl.)* **8**: 7–32.
- Reymann, K.G., U. Frey, R. Jork, and H. Matthies. 1988. Polymyxin B, an inhibitor of protein kinase C, prevents the maintenance of synaptic long-term potentiation in hippocampal CA₁ neurons. *Brain Res.* **440**: 305–314.
- Silva, A.J., C.F. Stemens, S. Tonegawa, and Y.-Y. Wang. 1992. Deficient hippocampal long-term potentiation in α -calcium-calmodulin kinase II mutant mice. *Science* **257**: 201–206.
- Smith, D.A., M. Browning, and T.V. Dunwiddie. 1993. Cocaine inhibits hippocampal long-term potentiation. *Brain Res.* **608**: 259–265.
- Stevens, C.F. 1993. Quantal release of neurotransmitter and long-term potentiation. *Cell* **72**: 55–63.
- Tocco, G., S. Maren, T.J. Shors, M. Baudry, and R.F. Thompson. 1994. Long-term potentiation is associated with increased [³H]AMPA binding in rat hippocampus. *Brain Res.* **573**: 228–234.
- Wang, J.-H. and D.-P. Feng. 1992. Postsynaptic protein kinase C essential to induction and maintenance of long-term potentiation in the hippocampal CA1 region. *Proc. Natl. Acad. Sci.* **89**: 2576–2580.
- Xie, X., T.W. Berger, and G. Barrionuevo. 1992a. Isolated NMDA receptor-mediated synaptic responses express both LTP and LTD. *J. Neurophysiol.* **67**: 1009–1013.
- . 1992b. Simultaneous expression of LTP by AMPA and NMDA receptor-mediated EPSP is of similar magnitude. *Abstr. Soc. Neurosci.* **18**: 628.5
- Zalutsky, R.A. and R.A. Nicoll. 1990. Comparison of two forms of long-term potentiation in single hippocampal neurones. *Science* **248**: 1619–1624.

Received July 16, 1996; accepted in revised form August 30, 1996.

Differential expression of short-term potentiation by AMPA and NMDA receptors in dentate gyrus.

X Xie, G Barrionuevo and T W Berger

Learn. Mem. 1996, **3**:

References

This article cites 41 articles, 11 of which can be accessed free at:
<http://learnmem.cshlp.org/content/3/2-3/115.full.html#ref-list-1>

License

Email Alerting Service

Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article or [click here](#).