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A Single 2-Spike Burst Induces GluR1-dependent Associative Short-term Potentiation: A Potential Mechanism for Short-term Memory

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Abstract

Recent work [Sanderson, D., Good, M.A., Skelton, K., Sprengel, R., Seeburg, P. H., Nicholas, J., et al. Enhanced long-term and impaired short-term spatial memory in GluA1 AMPA receptor subunit knockout mice: Evidence for a dual-process memory model. *Learning and Memory*, in press] showed that short-term memory (STM) is selectively reduced in GluR1 knockout mice. This raises the possibility that a form of synaptic modification dependent on GluR1 might underlie STM. Studies of synaptic plasticity have shown that stimuli too weak to induce long-term potentiation induce short-term potentiation (STP), a phenomenon that has received little attention. Here we examined several properties of STP and tested the dependence of STP on GluR1. The minimal requirement for inducing STP was examined using a test pathway and a conditioning pathway. Several closely spaced stimuli in the test pathway, forming a single brief burst, were sufficient to induce STP. Thus, STP is likely to be induced by the similar bursts that occur in vivo. STP induction is associative in nature and dependent on the NMDAR. STP decays with two components, a fast component (1.6 ± 0.26 min) and a slower one (19 ± 6.6 min). To test the role of GluR1 in STP, experiments were conducted on GluR1 knockout mice. We found that STP was greatly reduced. These results, taken together with the behavioral work of D. Sanderson et al. [Sanderson, D., Good, M. A, Skelton, K., Sprengel, R., Seeburg, P. H., Nicholas, J., et al. Enhanced long-term and impaired short-term spatial memory in GluA1 AMPA receptor subunit knockout mice: Evidence for a dual-process memory model. *Learning and Memory*, in press], provide genetic evidence that STP is a likely mechanism of STM.

INTRODUCTION

There are several candidate mechanisms for encoding short-term memory (STM). In prefrontal cortex, persistent firing in neurons has been proposed to underlie STM (Rawley & Constantinidis, 2009; Miller, Erickson, & Desimone, 1996; Goldman-Rakic, 1995; Fuster & Alexander, 1971). This persistent activity is generally thought to be due to reverberatory firing (Wang, 2001), although recent work suggests that intrinsic conductances may also be responsible (Sidiropoulou et al., 2009; Egorov, Hamam, Fransen, Hasselmo, & Alonso, 2002; Hasselmo, Fransen, Dickson, & Alonso, 2000; for a review, see Dash, Moore, Kobori, & Runyan, 2007).

At hippocampal synapses, the stimulation protocols that produce long-term potentiation (LTP) generally involves ~100 synaptic stimuli given at high frequency (20–200 Hz) (Bliss & Lomo, 1973). When fewer stimuli are given, the result is a transient potentiation termed

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short-term potentiation (STP) (Hanse & Gustafsson, 1992; Malenka, 1991; Anwyl, Mulkeen, & Rowan, 1989; Larson, Wong, & Lynch, 1986; McNaughton, 1982). STP could potentially serve as another mechanism for STM, especially those forms dependent on the hippocampus (Hartley et al., 2007; Kesner & Hopkins, 2006; Ranganath & Blumenfeld, 2005; Lee & Kesner, 2003; Mumby, Gaskin, Glenn, Schramek, & Lehmann, 2002; Eichenbaum, Otto, & Cohen, 1992).

The properties of STP have received little attention because of the focus of the field of synaptic plasticity on LTP. STP has often been considered synonymous with the early transient phase of LTP, but this remains to be fully tested. In this article, we have directly characterized STP by using an induction protocol weaker than required to produce LTP. We have sought to answer several questions relevant to the capability of STP to underlie STM. First, how short can one make the induction protocol and still produce STP? Answering this question would give us a perspective on whether STP can be induced by the firing patterns observed in the brain. Second, does the STP induced by brief stimuli have the associative properties vital for robust information storage (Sandberg, Tegner, & Lansner, 2003)? Third, what is the duration of STP, a property that would indicate the duration of STM that could be encoded? A final set of experiments was motivated by recent work showing that a form of STM in mice is selectively reduced in the GluR1 knockout (Sanderson et al., in press). GluR1 knockout reduces early stages of LTP (Jensen et al., 2003; Hoffman, Sprengel, & Sakmann, 2002; Zamanillo et al., 1999), but the effect on STP has not been previously determined. Our experiments show that STP is strongly reduced in the GluR1 knockout, supporting the hypothesis that STP is a mechanism for STM.

METHODS

Solutions

The following solutions were used for the experiment:

Artificial cerebrospinal fluid (ACSF) for extracellular recording in slices with GABAergic inhibition intact and with physiological levels of Mg and Ca (in mM): 124 NaCl, 2.5 KC1, 1.3 MgSO, 2.5 CaCl, 26 NaHCO, 1.25 NaHPO, and 10 dextrose.

ACSF for extracellular recording in slices with GABAergic inhibition blocked and with elevated Mg and Ca to reduce excitability consistent with established protocols for associative induction: 124 NaCl, 2.5 KC1, 4 MgSO, 4 CaCl, 26 NaHCO, 1.25 NaHPO, 20 dextrose, and 25 SYMBOL 109 “Symbol” 14M picrotoxin.

ACSF for slice preparation: 124 NaCl, 2.5 KC1, 4 MgSO, 2.5 CaCl, 26 NaHCO, 1.25 NaHPO, 20 dextrose, and 25 SYMBOL 109 “Symbol” 14M picrotoxin.

Animals

Long–Evans rats were purchased from Charles River Laboratories (Wilmington, MA) or Taconic Farms (Hudson, NY), and were used at ages P16–24. Mice lacking subunit 1 of the AMPA receptor (GluR1 knockout [KO] mice) were bred from pairs heterozygous for the mutation. Genotyping was performed following the procedure of (Jensen et al., 2003). Mice were used at ages P22–25 (juvenile) and P40–62 (adult), as indicated. Wild-type (WT) littermates were used as controls when available, otherwise age-matched WT animals from within the same colony were used. All procedures involving experimental animals were in accord with the recommendations of the American Veterinary Medical Association.

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Electrophysiology

Transverse hippocampal slices (300–350 µm thick) were prepared by vibratome in ice-cold high Mg^{2+} ACSF; then the CA3 region was removed by microdissection to prevent epileptiform events. Slices were incubated at room temperature in a humidified O_2/CO_2 saturated holding chamber for a minimum of 2 hours before recording. Field recordings were made from the stratum radiatum layer of CA1 in slices suspended on mesh in a submerged chamber at 30–31°C Electrodes (300–500 kΩ resistance) were filled with extracellular recording solution and stimulating electrodes were positioned on either side of the recording electrode. Stimulation was delivered via constant current stimulators (Isostim A320 or A360; WPI, Sarasota, FL) using a duration of typically 0.10–0.175 msec. For a small group of experiments, pulse duration was 0.35 msec. Control experiments indicated that pulse duration had no effect on STP kinetics or amplitude, or on field excitatory postsynaptic potential (fEPSP) waveforms. Stimulation strengths were set to obtain peak fEPSP amplitudes, which were 40% of the subthreshold maximum in experiments with inhibition blocked, and 50% in experiments with inhibition intact. Independence of the two pathways was identified by lack of facilitation when one pathway was stimulated 30 msec prior to the other, and additionally, post hoc by lack of potentiation in one pathway when LTP was induced in the other for all experiments in which LTP was induced. Pathways were stimulated in alternation with a test interval of 12 sec (0.083 Hz), unless otherwise indicated. Stable baselines were acquired for 20 min prior to the onset of induction paradigms. All experiments were interleaved with control experiments.

In experiments with GABAergic inhibition blocked by picrotoxin, STP induction consisted of a 2-stimulus burst (33 Hz) in a test pathway (Pathway 1) and a 5-stimulus burst (100 Hz) in an independent, “conditioning” pathway (Pathway 2). The onset of the 5-stimulus burst was delayed by 20 msec in all but the experiments comparing the efficacy of 1- versus 2-stimulus bursts. In two out of five of these efficacy experiments, Pathway 2 was stimulated with a longer burst (10 stimuli).

In experiments with GABAergic inhibition intact, stronger stimuli were used, as potentiation is more difficult to induce under these conditions (Wigstrom & Gustafsson, 1983). In these experiments, STP was induced using a 3-stimulus burst (200 Hz) in the test pathway and a 10-stimulus burst (200 Hz) in the “conditioning” pathway. Both bursts were presented simultaneously.

Typically, at least one population spike resulted from the STP induction protocol. Rarely, inadequate summation did not result in generation of a population spike, and STP induction failed under these conditions. LTP was also deficient in these slices. Data from these experiments were excluded. Slices from GluR1 KO mice were not deficient in the generation of population spikes and all data were included.

When LTP was induced in experiments with inhibition blocked in slices from rats, induction consisted of a 10-stimulus burst (100 Hz) presented four times at an interval of 6 sec (or 15 sec when test interval was 60 sec). When LTP was induced in experiments in mice and in rats when inhibition was intact, induction consisted of a theta-burst pattern of stimulation (TBS) consisting of five bursts (5 stimuli at 100 Hz) spaced 200 msec apart presented a total of three times spaced 10 sec apart. This protocol has been shown to be effective in the induction of LTP in GluR1 KO mice (Jensen et al., 2003; Hoffman et al., 2002; Zamanillo et al., 1999).

Data Acquisition and Analysis

An Axoclamp 2A (Axon Instruments, now Molecular Devices, Sunnyvale, CA), together with a differential AC amplifier (A–M Systems, Sequim, WA), or an Axoclamp 2B, together

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with a low-pass Bessel filter, LPF202A (Warner Instruments, Hamden, CT), was used to record field potentials and filter the data at 0.1 Hz low-frequency and between 1 and 5 kHz high-frequency cutoff. An ITC-18 Computer Interface (Instrutech, Port Washington, NY) was used to digitize the data (20 kHz) in real time, and provided the trigger for stimulation (as well as the duration of stimulation in later experiments). Data acquisition and analysis were performed using software written in Igor Pro (Wavemetrics, Lake Osewego, OR). fEPSP amplitude was evaluated as the difference between the mean of the baseline potential evaluated over ~20 msec prior to stimulus and the negative peak of the fEPSP over a ~1-msec window. Potentiation was calculated by normalization of fEPSP amplitudes by the average fEPSP amplitude calculated over the 5 min prior to induction. A significant reduction in noise resulted from the evaluation of potentiation using fEPSP amplitude rather than the fEPSP slope. The two measures of potentiation are essentially equivalent when fEPSPs are subthreshold (Abrahamsson, Gustafsson, & Hanse, 2007), as they are during STP and the plateau phase of LTP in this work.

In rats, curve fitting of the decay of potentiation as a function of time was performed starting from the peak of potentiation and typically ending at 30 min in order to confine the fit to the region with the highest signal-to-noise ratio. To avoid bias, curve fitting of data obtained at different test intervals was performed beginning at the same time point; ~70 sec for associative induction of STP and ~40 sec for 100 Hz burst. Double exponential fits were clearly found to be a better fit than single exponential fits when compared for a sample of representative experiments. Due to the inherently low signal-to-noise ratio of STP in the GluR1 KO mice, fits were performed to the averaged data, rather than individual experiments for the KO data and the WT control, and extended out to 40 min. Constants derived from these fits are stated as fit parameters ± 95% confidence interval. Elsewhere, statistical significance was calculated in Excel (Microsoft, Redmond, WA), using Student's two-tailed *t* test, as all distributions were found to be normal. Error bars on plots indicate *SEM* and means are stated as ±*SEM*, unless otherwise indicated.

Chemical Reagents

Reagents were purchased from Fischer Scientific (Pittsburgh, PA), with the exception of picrotoxin (Sigma-Aldrich, St. Louis, MO) and DL-APV (Ascent Scientific, Princeton, NJ).

RESULTS

We first determined the minimal stimulus necessary to evoke STP in slices in which GABAergic inhibition was blocked. We modified a protocol for the induction of associative LTP to induce STP (Colino, Huang, & Malenka, 1992; Malenka, 1991; Gustafsson & Wigstrom, 1986). In our protocol, a stimulus in a test pathway (33 Hz, 2 stimuli) was given together with stimulation in an independent (conditioning) pathway (100 Hz, 5 stimuli; see inset, Figure 2). We investigated the number of stimuli in the test pathway required to produce STP. A single stimulus resulted in little potentiation (Figure 1). However, when the single stimulus was replaced by a 2-stimulus burst (33 Hz), robust STP was elicited (143 ± 21% for a 2-stimulus burst; 110 ± 8.3% for a single stimulus; $n = 8$, $p < .001$). This indicates that the local biochemical reactions that underlie STP can be triggered by the brief bursts that are known to occur in hippocampal pyramidal cells (Ranck, 1973) (provided other inputs produce depolarization equivalent to that produced by the conditioning pathway).

The decay of STP (~20 min) is generally consistent with previous observations (Colino et al., 1992; Malenka, 1991; Gustafsson & Wigstrom, 1986). This decay was not due to a deficiency in the capacity for sustained potentiation because we were subsequently able to induce LTP by stronger stimulation (10 stimuli at 100 Hz presented 4 times at 6 sec) in the same preparations (Figure 2).

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The Hebbian model for learning sets forth that memory must be encoded by an associative process. We tested whether STP induced by our 2-stimulus burst protocol fulfills this requirement. A 2-stimulus burst in the test pathway without stimulation of the conditioning pathway did not elicit potentiation (99.2 ± 2.4%; $n = 4$; data not shown). Furthermore, if a burst in the conditioning pathway was made asynchronous with the test pathway (following the 2-stimulus burst by 2.5 sec), no potentiation resulted (Figure 3A; see also Figure 4) (107 ± 7.7% with asynchronous stimulation; 158 ± 18% with synchronous stimulation; $n = 8$, $p < .001$). STP thus has associative properties.

In vivo, the extent of inhibition is reduced during exploration (Wilson & McNaughton, 1993). Thus, the conditions of low inhibition utilized above may resemble the conditions during learning. However, it is also possible that considerable inhibition remains and so we sought to characterize STP under conditions of full inhibition. We therefore tested whether associative STP can still be induced by brief bursts under conditions in which GABAergic inhibition is not reduced by picrotoxin, and with a more physiological concentration of extracellular Mg^{2+} and Ca^{2+}. A 3-stimulus burst (200 Hz) in a test pathway synchronized with stronger stimulation in an independent pathway (200 Hz, 10 stimuli) produced STP (120 ± 2.5%, $n = 8$) (Figure 4), which was statistically significant from the baseline (101 ± 6.0%, $p < .001$). Thus, brief high-frequency bursts are capable of inducing STP even in the presence of GABAergic inhibition. As with the STP induced when GABAergic inhibition is reduced, this STP was associative, as a 3-stimulus burst in the test pathway without synchronized stimulation in the conditioning pathway did not elicit potentiation (104 ± 1.2%, $n = 8$). Nor was the decay of STP a result of a deficiency in the capacity for potentiation induced by a theta-burst protocol. LTP was significant until at least 40 min compared to the baseline (baseline, 101 ± 6.0%; LTP at 30 min, 134 ± 9.6%, $n = 8$, $p < .001$). Thus, even with inhibition intact, associative STP could still be induced by brief bursts, lending further support to the idea that the requirements for induction of associative STP may readily be met in vivo.

The molecular mechanism believed to underlie the associativity of LTP is the NMDA receptor (NMDAR), which requires both presynaptic release of glutamate and post-synaptic depolarization to allow significant influx of Ca^{2+} (Mayer & Westbrook, 1987; Mayer, Westbrook, & Guthrie, 1984; Nowak, Bregestovski, Ascher, Herbet, & Prochiantz, 1984). We tested whether STP induced with the short bursts used in our induction protocol (with GABAergic inhibition reduced) was affected by NMDAR antagonist (DL-APV at 200 μM). Potentiation was fully blocked with no evidence of post-tetanic potentiation, the nonassociative presynaptic facilitation evoked by tetani (Figure 3B) (96.6 ± 1.1% with APV; 153 ± 4.2% without APV; $n = 6$, $p < .001$). Thus, associative STP induced by a single burst is an NMDAR-mediated process. Similar results have been reported for STP using nonassociative induction protocols (Colino et al., 1992; Malenka, 1991; Anwyl et al., 1989; Larson & Lynch, 1988; Gustafsson & Wigstrom, 1986).

The duration of memories that could be stored by STP would be determined by the time course of the decay of potentiation back to baseline. We performed kinetic analysis of the decline of STP induced when GABAergic inhibition was reduced; both fast and slow components were evident, as indicated by the double exponential fit to the data (Figure 5A and B). A representative experiment is shown (Figure 5A), together with the double exponential fit in which the time constants governing the decay were 1.5 ± 0.23 min for the fast component and 11 ± 3.4 min for the slow component. Fit parameters derived from six individual experiments are shown in Figure 5B. The time constants governing the decay were 1.6 ± 0.26 min for the fast component and 19 ± 6.6 min for the slow component ($n = 6$; test stimulus interval, 12 sec). In these experiments, there was negligible LTP (100.3 ±

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2.8%). The two components of STP contributed equally at the peak of potentiation (fast = 120 ± 3.6%; slow = 120 ± 0.9%; $n = 6$) (Figure 5C).

The decline of STP might be due to an activity-independent intrinsic process or, alternatively, to erasure produced by the test pulses. Studies of the decline of the transient phase of LTP suggested that the decline was dependent on the presence of test pulses (Volianskis & Jensen, 2003; Xiao, Niu, & Wigstrom, 1996). To determine whether the decline of STP is dependent on test pulses, we altered the interstimulus interval (from 12 to 60 sec). The results show that this did not significantly change the time constants of the decay of STP (fast = 2.3 ± 0.48 min; slow = 34 ± 11 min; $n = 5$, $p = .21$ and .22, respectively; Figure 5A and B). We examined the same question using a stronger nonassociative induction protocol (5 stimuli at 100 Hz), which elicits a small persistent component, and again found no indication of activity-dependent erasure of the initial potentiation (Figure 5C). Taken together, these results suggest that the decay of STP is determined by activity-independent processes.

Previous work on GluR1 knockout (KO) showed that the early transient phase of LTP was absent in these mice; in contrast, LTP at 25 min was unaffected (Jensen et al., 2003; Hoffman et al., 2002; Zamanillo et al., 1999). On the assumption that STP accounts for the early phase of LTP, these results suggest that STP has a strong dependence on GluR1. We have used our protocol for evoking STP (without LTP) to directly test the dependence of STP on GluR1. As shown in Figure 6A and B, adult GluR1 KO mice displayed a pronounced deficit in STP [peak potentiation: 113 ± 3.5% ($n = 7$) vs. 136 ± 9.1% in the WT ($n = 8$)]. STP peak amplitude was reduced to 36% of the control; moreover, the remaining STP decayed faster (Figure 6B, see caption for statistics). Thus, the effectiveness of STP as a synaptic memory is greatly reduced in the GluR1 KO.

Under some induction conditions, GluR1 contributes only to the early phase of LTP (Jensen et al., 2003; Hoffman et al., 2002; Zamanillo et al., 1999), but there is also evidence that it can make a contribution to LTP under other conditions (Frey, Sprengel, & Nevian, 2009; Jensen et al., 2003; Kolleker et al., 2003; Hoffman et al., 2002; Zamanillo et al., 1999). To examine this issue under our conditions, we stimulated slices from adult GluR1 KO mice with a theta-burst protocol (Jensen et al., 2003; Kolleker et al., 2003; Hoffman et al., 2002; Zamanillo et al., 1999). In WT animals, induction resulted in a large initial potentiation, which decayed to a plateau of LTP (Figure 6A). This initial potentiation was greatly reduced in the GluR1 KO, with the peak of the initial potentiation being 123.5 ± 9.1% ($n = 7$) compared with 220 ± 49% ($n = 8$) in the WT. In the KO, potentiation developed with a biphasic time course (Figure 6A); the initial potentiation decayed rapidly, but then started to rise at 2.5 min until a stable level was reached at 5 min. This potentiation persisted for at least 40 min (LTP), and was 34% of the WT level [120 ± 10% for the GluR1 KO ($n = 7$); 158 ± 14% for the WT ($n = 8$), respectively]. Taken together, these results suggest that both STP and LTP are affected in the GluR1 KO, but not equally: STP and the early transient phase of LTP are more strongly affected than the plateau phase of LTP, consistent with a model that postulates a special role for GluR1 in STP (as compared to LTP) (Lisman & Raghavachari, 2006).

Evidence has suggested that in juvenile mice, a splice variant of GluR2, termed GluR2-long, can substitute for GluR1 because GluR1 and GluR2-long each have a long C-terminal tail (Kolleker et al., 2003; Shi, Hayashi, Esteban, & Malinow, 2001). Thus, substitution could potentially result in WT levels of STP in the juvenile GluR1 KO. We compared STP in juvenile and adult GluR1 KO mice. A trend suggestive of a modest increase in potentiation in the juvenile relative to the adult was seen in the first 2 min after STP induction, but these levels did not approximate those seen in the WT. Potentiation also did not approach WT

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levels in the juvenile KO after LTP induction. These data suggest that even in juvenile animals, STP is strongly dependent on GluR1, and further, that LTP is not fully dependent on GluR1 in either juveniles or adults in the WT (Romberg et al., 2009).

DISCUSSION

We have examined several properties of STP. Most importantly we have found that STP is strongly decreased in the GluR1 knockout. LTP is less affected than STP, consistent with previous work on the GluR1 knockout showing that nearly normal LTP can be induced by several different induction protocols (Frey et al., 2009). The deficit in STM in the GluR1 KO takes on special significance because recent work provides evidence that STM is selectively reduced in the same KO (Schmitt et al., 2004; Schmitt, Deacon, Seeburg, Rawlins, & Bannerman, 2003; Reisel et al., 2002). This has been demonstrated using the spontaneous alternation paradigm in which an animal spontaneously selects one of two arms to explore. When presented with a choice of arms a short time later (< 1 min), the WT animal exhibits a pronounced preference for the unexplored arm, whereas the GluR1 KO chooses at random, suggesting no memory of the recent exploration (Sanderson et al., 2007; Bannerman et al., 2004). The same animals that show poor STM, however, show enhanced memory when tested at 24 hours, suggesting that this form of long-term memory is not dependent on the GluR1 (or STM) (Sanderson et al., in press). The GluR1 KO mice are also capable of learning and using cues that depend on spatial reference memory (Schmitt et al., 2003; Zamanillo et al., 1999), but only as long as the cues are present at the time of choice (Schmitt et al., 2003, 2004; Reisel et al., 2002). These findings indicate that the GluR1 KO does not exhibit a global deficit in learning, but instead exhibits a specific deficit in STM. This demonstration of the GluR1-dependence of STM, taken together with our demonstration of the GluR1-dependence of STP, supports the hypothesis that STP could underlie at least some forms of STM.

There are likely to be multiple mechanisms of STM. Indeed, there is clear evidence in neocortex that persistent firing occurs during some forms of STM tasks and could therefore be the mechanism of STM (Goldman-Rakic, 1995; Funahashi, Bruce, & Goldman-Rakic, 1989; Fuster & Alexander, 1971). Such persistence could occur both for novel or familiar items, even without synaptic modification (Lisman, Fellous, & Wang, 1998). The cellular and molecular mechanisms of persistent firing remain unclear (see Introduction), and thus, it has not yet been possible to test the role of particular molecular mechanisms underlying this persistent firing using genetic manipulation or behavioral studies on transgenics.

Properties of STP and Their Relevance to Short-term Memory

Our results show that STP can be induced by very short stimulation protocols. The test pathway is of particular importance because STP occurs in this pathway and must be mediated by local biochemical events triggered as a result of NMDAR-mediated Ca^{2+} entry (see below). Our results show that a single minimal burst consisting of only two spikes in the test pathway serves as a sufficient trigger. Pyramidal cells in the hippocampus produce bursts consisting of two to seven spikes (Ranck, 1973), a pattern of firing which they have in common with neurons in many other brain regions (Gemmell, Anderson, & O’Mara, 2002; Schwindt, O’Brien, & Crill, 1997). Our results indicate that even the shortest of such bursts are sufficient to provide this trigger. Longer ones may induce LTP (Remy & Spruston, 2007). It has been previously shown that a single brief burst can induce LTP under special neuromodulatory conditions that enhance plasticity (Huerta & Lisman, 1995). We emphasize, however, that the ability to induce STP using a short burst does not require any special neuromodulatory conditions (either in the presence or absence of GABAergic inhibition). The induction of associative STP also requires the depolarization produced by the conditioning pathway. In our experiments, this depolarization was achieved by 5 to 10

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stimuli given within ~60 msec (i.e., within the time frame of a theta cycle). Such short trains occur in the hippocampus. However, we suspect that the depolarization required for associative STP could arise by other patterns of temporal/spatial integration. In the current protocol, the number of synapses activated during a single stimulus is insufficient to produce a spike. Thus, if a greater number of inputs were active during in vivo events, they could presumably produce the depolarization sufficient for STP with less repetition than we utilized in the conditioning pathway.

The associative properties of STP make it a particularly appealing candidate mechanism for STM. Consistent with previous results using a slightly different protocol (Colino et al., 1992; Malenka, 1991; Anwyl et al., 1989; Larson & Lynch, 1988; Gustafsson & Wigstrom, 1986), we found that STP induction is associative. Our induction by a single short burst (~60 msec) has a greater resemblance to in vivo activity than protocols that require repeated trains of stimuli over the course of ~40 sec. We found that STP is dependent on the NMDA receptor, as previously reported (Colino et al., 1992; Malenka, 1991; Anwyl et al., 1989; Larson & Lynch, 1988; Gustafsson & Wigstrom, 1986). An important action of the NMDAR is to produce intra-cellular Ca^{2+} entry (Kullmann, Perkel, Manabe, & Nicoll, 1992; Malenka, Lancaster, & Zucker, 1992). Thus, STP has NMDAR-dependent Hebbian properties similar to LTP (Kelso, Ganong, & Brown, 1986). Another candidate mechanism for STM, presynaptic facilitation (Mongillo, Barak, & Tsodyks, 2008), lacks this property. Associativity endows a recurrent neural network with the attractor properties that allow for pattern completion, such as that seen with LTP. In the field of human memory, there has been considerable debate on whether STM and long-term memory depends on fundamentally different mechanisms (reviewed in Cowan, 2008). According to one view, STM depends on a multi-item buffer that stores memories through persistent firing, whereas long-term memory depends on associative synaptic plasticity (reviewed in Usher, Davelaar, Haarmann, & Goshen-Gottstein, 2008). According to a second view, both short- and long-term memory depend on associative synaptic modifications (reviewed in Sederberg, Howard, & Kahana, 2008). Our results support the idea that some forms of STM depend on synaptic modification. An important implication is that STP could make attractor states possible; thus, provided that STP has not decayed, the memory could be reactivated. Such reactivation could be the basis for replay events that are necessary for consolidation of the memory into a persistent form (reviewed in Suzuki, 2006).

Because STP depends on the activation of the NMDAR (Colino et al., 1992; Malenka, 1991; Anwyl et al., 1989; Larson & Lynch, 1988; Gustafsson & Wigstrom, 1986) (see Figure 3B), the question of whether STM is inhibited by NMDAR antagonists is relevant. If STM was not blocked by the NMDAR antagonist, STP could be ruled out as a mechanism of STM. However, several reports in both human and animal experiments indicate that at least some forms of working memory are strongly affected by such antagonists (Adler, Goldberg, Malhotra, Pickar, & Breier, 1998; Krystal et al., 1994; for a review, see Fletcher & Honey, 2006).

The time span of usable information encoded by STP is dependent on the onset time of STP and the time constant (s) of its subsequent decay. The onset of potentiation has been reported as 2–3 sec after induction, and is independent of the stimulation strength used for induction (Gustafsson, Asztely, Hanse, & Wigstrom, 1989). Thus, although STP is likely dependent on modifications of AMPA channel function (see below), STP can develop within seconds, and thus, be useful in memory tasks where stored information must be accessed with only several seconds delay. The potential duration of STMs encoded by STP would be limited by its decay back to baseline. Kinetic analysis of this decay revealed two components, one with a time constant of 1.6 ± 0.26 min and another with a time constant of 19 ± 6.6 min. The time course of the decay of human STM has been very difficult to

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determine because persistence may be due to rehearsal and because other memories may interfere with recall (proactive and retroactive interference) (reviewed in Dewar, Cowan, & Sala, 2007). Recent work that has minimized these factors suggests that spontaneous decay of memory is in the minute range (Cowan & AuBuchon, 2008; Nairne, 2002), and not ~10 sec as had been previously thought (Peterson & Peterson, 1959). This time frame is consistent with a role for STP in STM.

Molecular Basis of GluR1 Action in STP

Earlier work with the GluR1 KO has shown that GluR1 is required for the early transient phase of LTP (Jensen et al., 2003; Hoffman et al., 2002; Zamanillo et al., 1999), but the effect of this KO on isolated STP has not been previously examined. Our results show that STP is greatly reduced in the GluR1 KO. This suggests that STP and the early transient phase of LTP may indeed have common mechanisms, as has been suspected (for a review, see Malenka & Nicoll, 1993). However, our results also point to difficulties in attributing aspects of early LTP to STP. The decay of the early transient phase of LTP is activity-dependent (Volianskis & Jensen, 2003; Xiao et al., 1996); in contrast, we have found that the decay of STP is not. One possibility for the sensitivity of the early phase of LTP to subsequent activity may be that it is the strong stimulation used for LTP induction that results in activity-dependent potentiation. This subsequent activity could potentially alter the development of LTP, or could trigger the reversal of potentiation, thereby contributing to the initial decaying component of LTP.

The mechanism by which GluR1 contributes to STP remains unclear. GluR1-dependent potentiation could occur either by a rapid change in the number of channels at the synapse or by the phosphorylation of the GluR1 channels already in the synapse at sites that are known to increase channel conductance (Banke et al., 2000; Derkach, Barria, & Soderling, 1999). Specific phosphorylation sites of GluR1 have been mutated in several studies (Lee et al., 2003, 2007). Although reduced LTP is apparent in these transgenics, none exhibit the specific deficit in early LTP seen in the GluR1 KO. Thus, if phosphorylation is important, it would have to involve other phosphorylation sites on GluR1 (Boehm et al., 2006).

Although most physiological and biochemical experiments on the role of GluR1 in synaptic plasticity have been conducted in the hippocampus, work on the GluR1 KO has revealed its involvement in plasticity in barrel cortex (Hardingham & Fox, 2006). In the GluR1 KO, the induction of LTP in this region bears a striking resemblance to that seen in the CA1 region of the hippocampus (Hoffman et al., 2002), exhibiting significant attenuation during the first 10 min followed by nearly normal levels of LTP at later times. Thus, GluR1-dependent STP may be a general mechanism rather than a solely hippocampal process.

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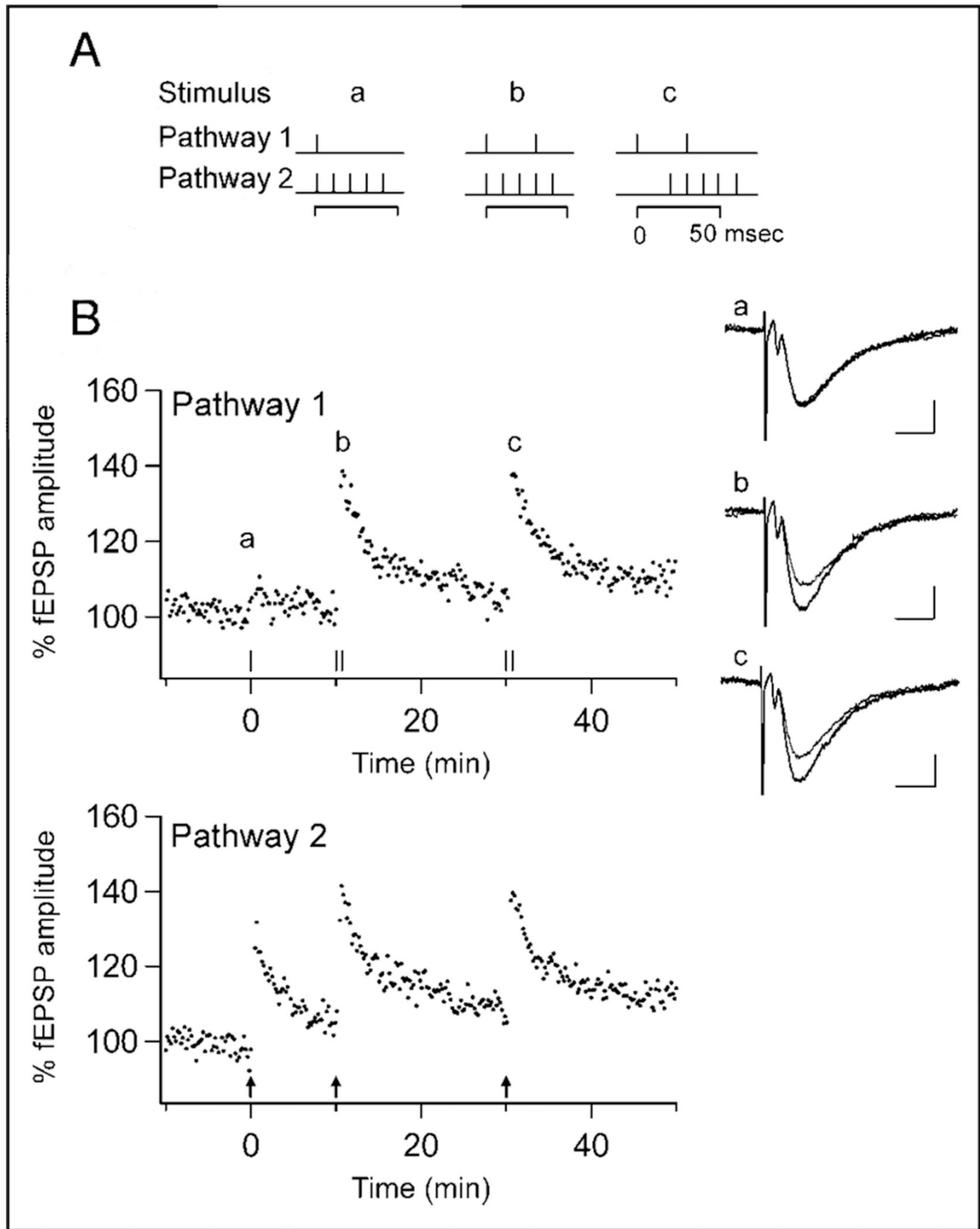

Figure 1.

Single 2-spike burst induces robust STP. (A) Stimulation paradigms used at times corresponding to letters shown on plot below. (B) At “a,” induction consisted of coincident stimulation of a single subthreshold fEPSP (indicated by single vertical line, Pathway 1) with a brief burst (5 stimuli at 100 Hz) (indicated by arrow in Pathway 2) in an independent pathway. At “b,” two test stimuli (33 Hz, indicated by closely spaced vertical lines) were used in Pathway 1. At “c,” the two test stimuli preceded the 100-Hz burst by 20 msec. Inset is an overlay of fEPSPs from Pathway 1 just prior to (thin trace) and following (thick trace) induction paradigms at “a,” “b,” and “c.” Calibration bars correspond to 5 msec and 200 μV.

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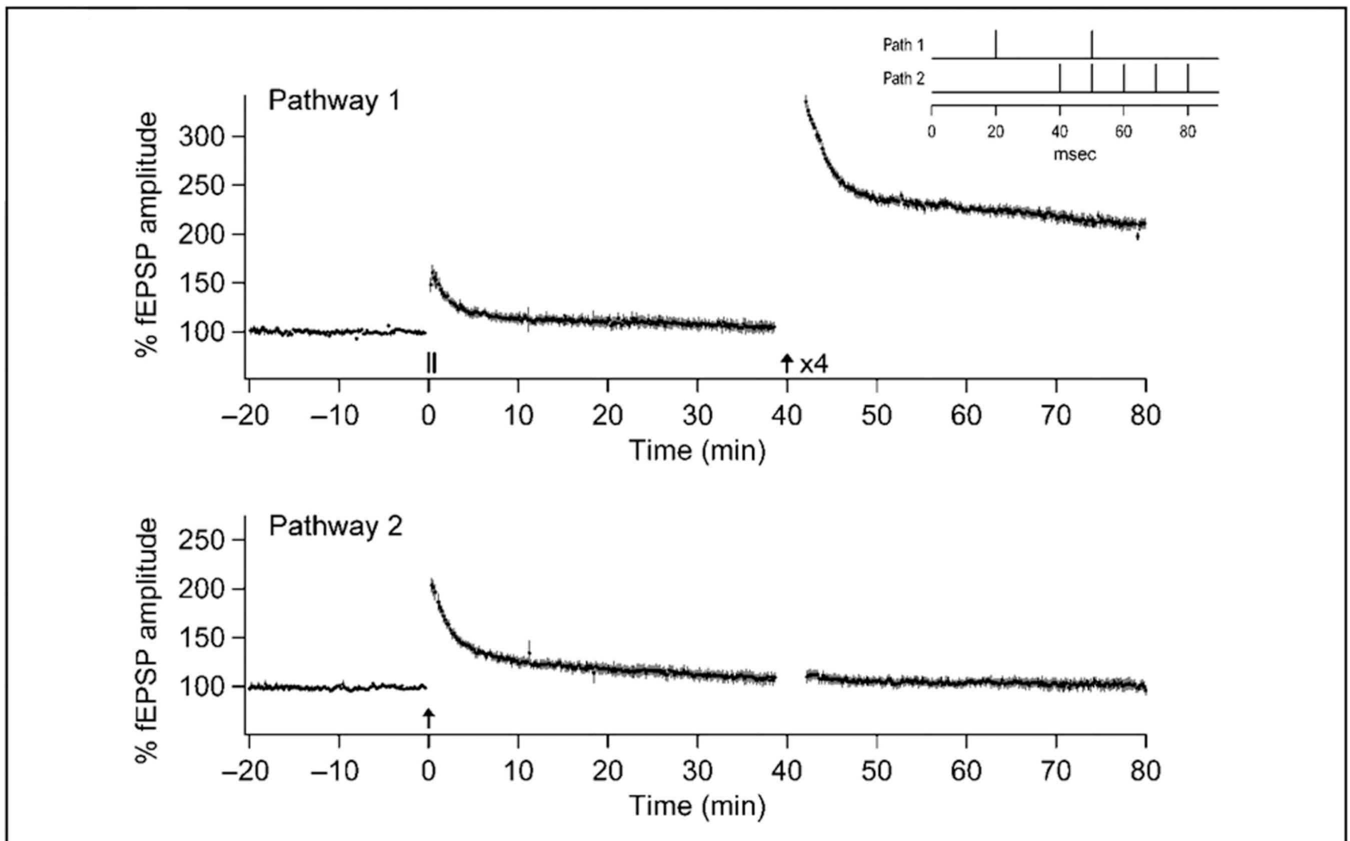

Figure 2.

STP is not a deficit in capacity for persistent potentiation (LTP). Average of five experiments in which STP was induced at time 0 (induction paradigm shown in inset) and LTP was subsequently induced at 40 min (indicated by arrow) by 10 stimuli at 100 Hz presented four times (6 sec apart). Error bars denote *SEM*. Test interval, 12 sec.

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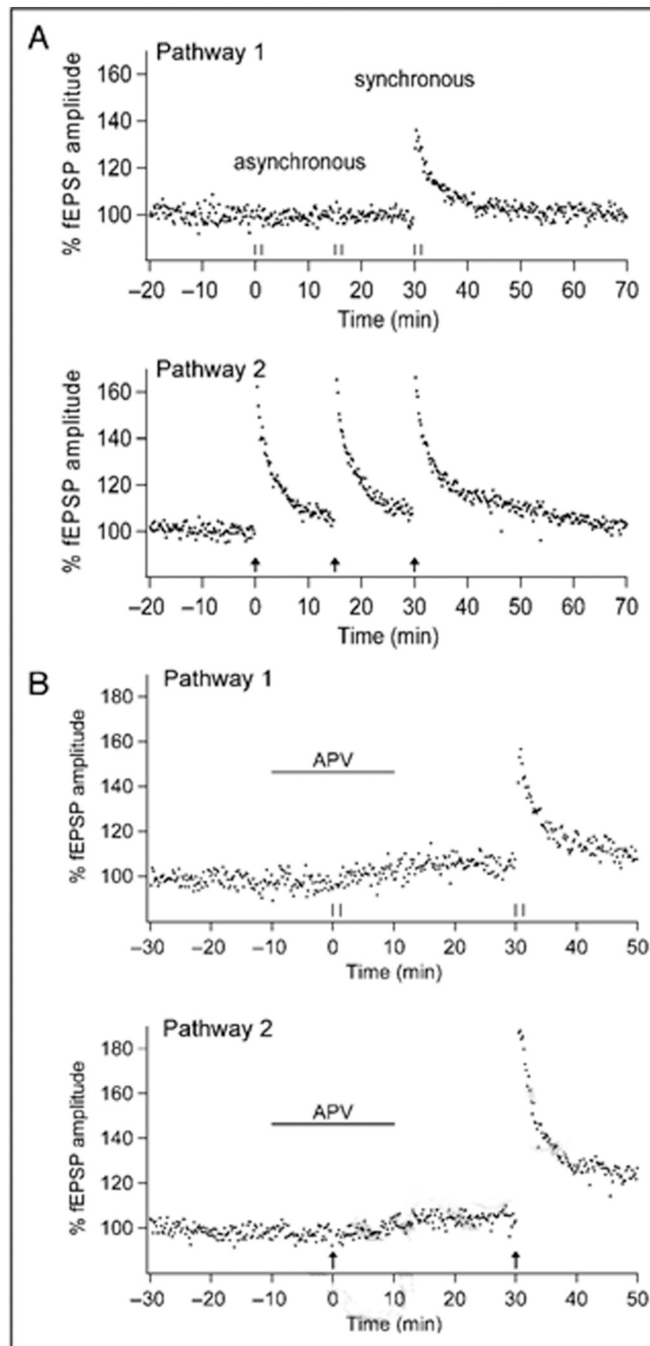

Figure 3.

STP induced by single 2-spike burst is associative and NMDAR-dependent. (A) Data from a single experiment in which a single 2-spike burst was given in Pathway 1 and the 100-Hz burst in Pathway 2 followed 2.5 sec later (at times 0 and 15 min). No potentiation resulted in Pathway 1. At 30 min, the delay was reduced to 20 msec and STP resulted. (B) Data from a single experiment in which the NMDAR antagonist, DL-APV (200 μM), was applied (from −10 to 10 min, designated by horizontal bar) and the 2-spike STP induction paradigm was given in its presence (time 0). No potentiation resulted. Following washout of APV, the same induction paradigm (time 30) resulted in STP, indicating that STP is dependent upon NMDAR.

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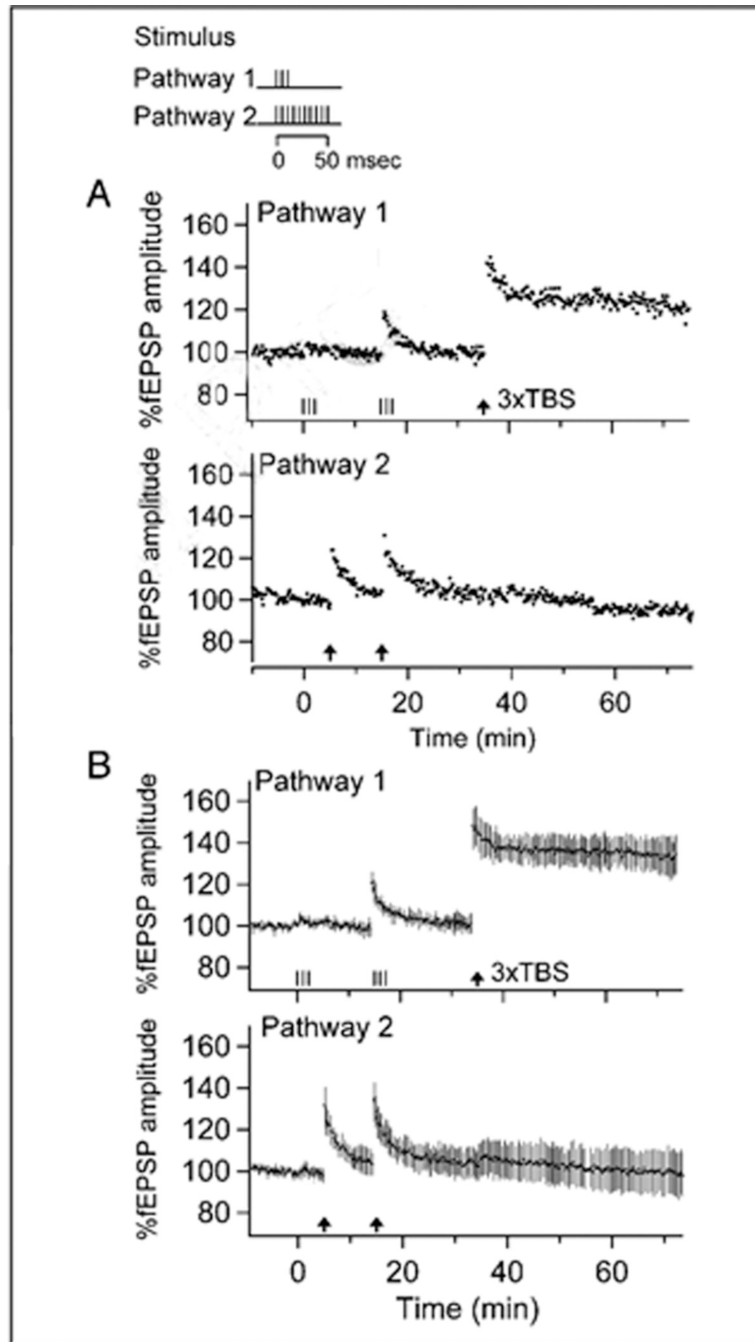

Figure 4.

Properties of STP with inhibition intact. (A) Data from a single experiment in which associative STP was induced by coincident stimulation of a 3-spike burst (200 Hz) in Pathway 1 and a 10-spike burst (200 Hz) in Pathway 2 at 15 min (induction paradigm shown in inset). Neither the single 3-spike burst, given in Pathway 1 at time 0 (indicated by closely spaced vertical lines in Pathway 1), nor the 10-spike burst, given in Pathway 2 at 5 min (indicated by arrow in Pathway 2), resulted in potentiation in Pathway 1. LTP was induced using a theta-burst induction protocol at 35 min. Test interval, 12 sec. (B) Cumulative average of experiments, as in A, in which associative STP was induced with inhibition intact (n = 8). Error bars denote *SEM*.

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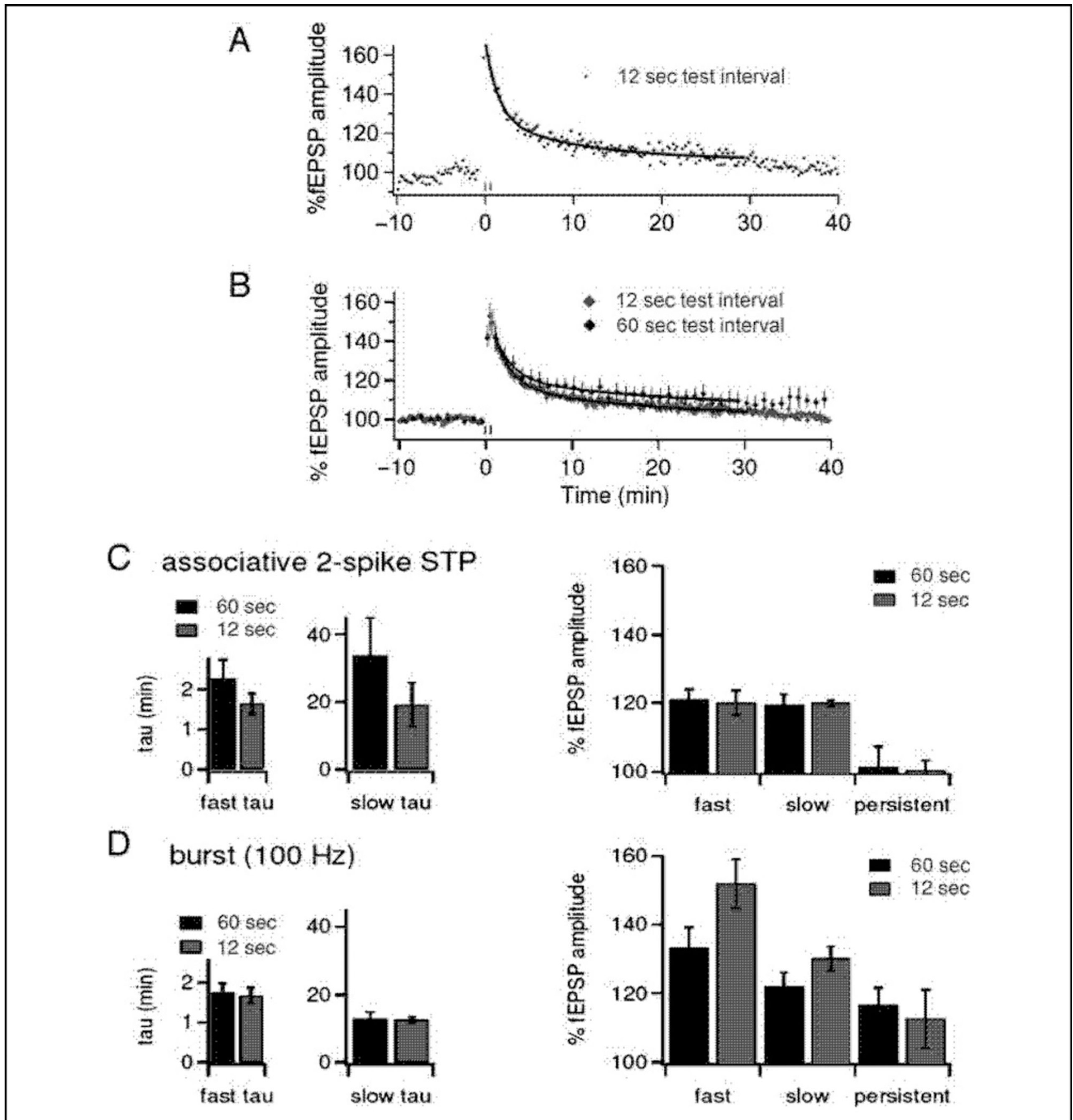

Figure 5.

Kinetic analysis of STP reveals fast and slow components. (A) Data from a single experiment in which STP was induced at time 0 when the test interval was 12 sec. Solid line indicates double exponential fit to the data. (B) Cumulative average of experiments in which STP was induced when the test interval was 12 sec (n = 6) (closed diamonds) or 60 sec (n = 5) (open diamonds). Solid lines indicate double exponential fits to the data. Error bars denote *SEM*. (C) Bar graphs indicating average parameters of double exponential fits to individual experiments at different test intervals. Fit parameters were not significantly different at different test intervals. For associative 2-spike STP: 12 sec test interval (n = 6), 60 sec test interval (n = 5). (D) As in B, but for response to burst (5 stimuli at 100 Hz). Fit

parameters were not significantly different at various test intervals: 12 sec and 60 sec (n = 4).

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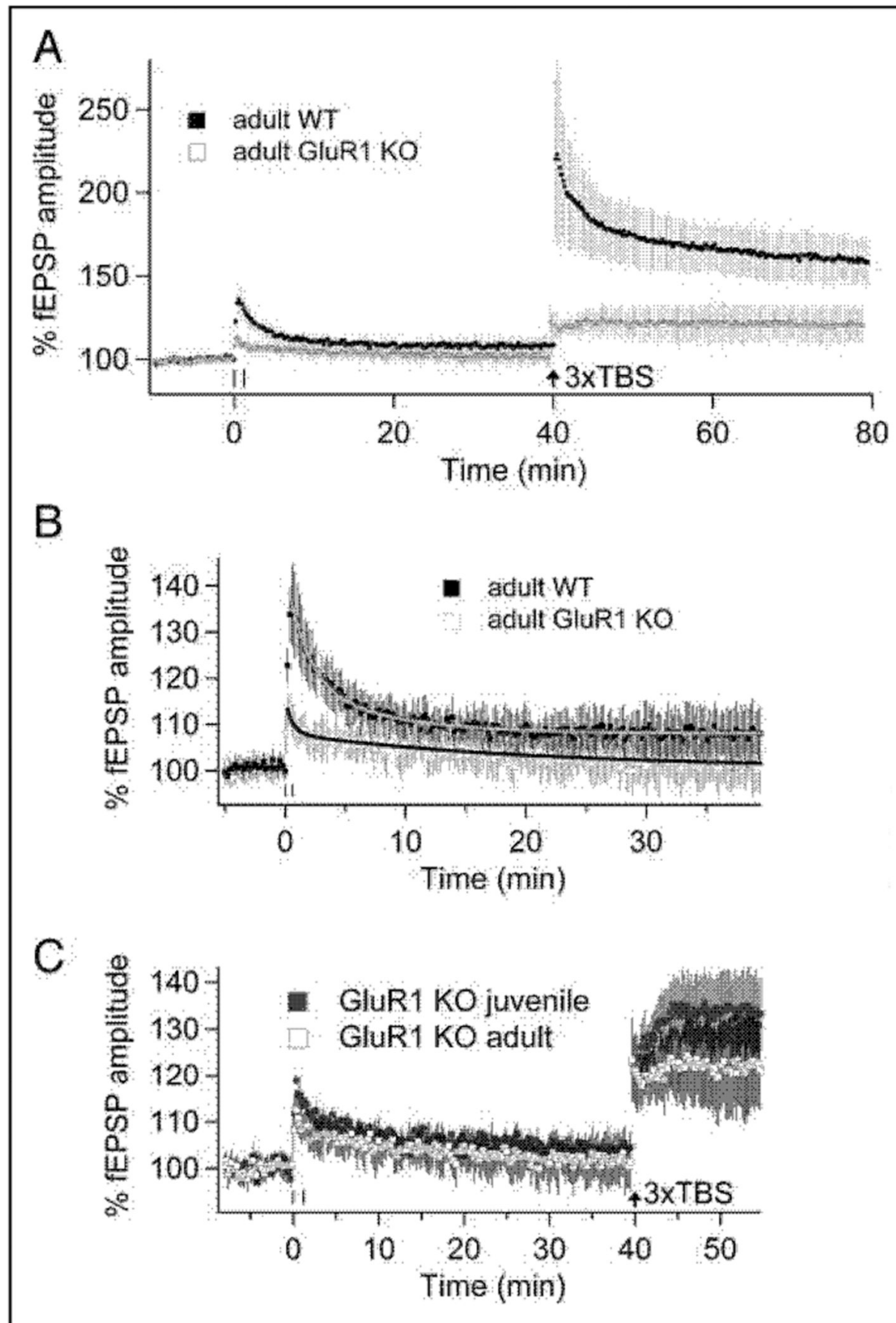

Figure 6.

STP has a GluR1-dependent component. STP was diminished in the adult GluR1 KO mouse relative to WT. (A) Response to STP induction paradigm at time 0 in adult WT mice (filled squares, *n* = 8), ages P40–62 and GluR1 KO mice (open squares, *n* = 7), ages P40–62. At time 40 LTP was induced using a theta-burst induction protocol. (B) Data from A showing STP on an expanded scale, with solid lines indicating double exponential fits to the data. In the GluR1 KO, the amplitude of the fast component was 27% of the WT [105 ± 1.5% (*n* = 7), as compared to 120 ± 4.6% in the WT (*n* = 8); note, numbers in this section are fit parameters ± 95% confidence intervals]. The contribution of the fast component to STP was further reduced because it displayed a more rapid decay (0.56 ± 0.3 vs. 1.9 ± 0.48 min in the

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WT). The slow component was very small and not substantially changed in the KO. (C) Response to STP induction paradigm at time 0 in adult GluR1 KO mice (open squares, n = 7), ages P40–62 and juvenile GluR1 KO mice (gray squares, n = 6), ages P22–25. At 40 min, LTP was induced using a theta-burst induction protocol.