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Long-term plasticity of dendritic integration is induced in parallel with long-term potentiation (LTP) or depression (LTD) based on presynaptic activity patterns. It is, however, not clear whether synaptic plasticity induced by temporal pairing of pre- and postsynaptic activity is also associated with synergistic modification in dendritic integration. We show here that the spike timing-dependent plasticity (STDP) rule accounts for long-term changes in dendritic integration in CA1 pyramidal neurons *in vitro*. Positively correlated pre- and postsynaptic activity (delay: +5/+50 ms) induced LTP and facilitated dendritic integration. Negatively correlated activity (delay: −5/−50 ms) induced LTD and depressed dendritic integration. These changes were not observed following positive or negative pairing with long delays (> ±50 ms) or when NMDA receptors were blocked. The amplitude–slope relation of the EPSP was facilitated after LTP and depressed after LTD. These effects could be mimicked by voltage-gated channel blockers, suggesting that the induced changes in EPSP waveform involve the regulation of voltage-gated channel activity. Importantly, amplitude–slope changes induced by STDP were found to be input specific, indicating that the underlying changes in excitability are restricted to a limited portion of the dendrites. We conclude that STDP is a common learning rule for long-term plasticity of both synaptic transmission and dendritic integration, thus constituting a form of functional redundancy that insures significant changes in the neuronal output when synaptic plasticity is induced.

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Activity-dependent plasticity of intrinsic neuronal excitability was originally described in invertebrates but has also been reported under different experimental conditions in many mammalian neurons (review in Hansel *et al.* 2001; Zhang & Linden, 2003; Daoudal & Debanne, 2003*a*). It is a persistent form of neuronal modification that might encode novel information to modify a behaviour. However, it is not yet clear whether intrinsic plasticity corresponds to an additional level of plasticity that makes understanding of information storage in the brain more complex or rather if it can be incorporated into a *general framework* in which *synaptic* and *non-synaptic* plasticity interact coherently and harmoniously. To address this major question it is important to define the learning rules of intrinsic plasticity and the nature of its interaction with synaptic plasticity.

In the hippocampus, homosynaptic long-term synaptic potentiation (LTP) induced by high-frequency presynaptic stimulation is associated with enhanced firing probability of the postsynaptic neurons in response to a given excitatory synaptic input (Bliss & Lømo, 1973; Bliss *et al.* 1973; Andersen *et al.* 1980; Abraham *et al.* 1987). This component has been called EPSP-to-spike potentiation (E–S potentiation) which is complementary to synaptic potentiation and functionally important. E–S potentiation is partly independent of $GABA_A$ and $GABA_B$ receptor-mediated synaptic inhibition (Daoudal *et al.* 2002; Staff & Spruston, 2003; Marder & Buonomano, 2003), indicating that E–S potentiation may involve long-lasting modulation of intrinsic voltage-gated conductances. GABA receptor-independent E–S potentiation is input specific (Hess & Gustafsson, 1990; Daoudal *et al.* 2002), suggesting that the underlying changes in excitability might be restricted to a small region of the dendrites. In accordance with the Bienenstock *et al.* (1982) theory of synaptic modification (or BCM rule), low-frequency presynaptic stimulation (1–5 Hz) produced long-term synaptic depression (LTD) (Artola *et al.* 1990; Dudek & Bear, 1992; Mulkey & Malenka, 1992). Most

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importantly, this form of LTD is associated with a GABA receptor-independent and input-specific depression in E–S coupling in CA1 pyramidal neurons (Daoudal *et al.* 2002). Thus, the BCM learning rule is valid for both synaptic changes and plasticity of dendritic integration in the hippocampus.

Synaptic plasticity is also induced associatively in hippocampal and cortical neurons. Based on Hebbian learning rules, positively correlated pre- and postsynaptic spiking activity (pre before post) leads to the induction of LTP (Gustafsson *et al.* 1987) whereas negative correlation (post before pre) induces LTD (Debanne *et al.* 1994, 1996, 1998; Markram *et al.* 1997; Bi & Poo, 1998; Feldman, 2000; review in Dan & Poo, 2006). Changes in intrinsic excitability have been reported following LTP induced by STDP-like protocols (Jester *et al.* 1995; Wang *et al.* 2003; Frick *et al.* 2004; Xu *et al.* 2005; Fan *et al.* 2005). However, it is not yet clear whether plasticity of dendritic integration follows the temporal specificity of the STDP learning rule and respects the input specificity conveyed by synaptic plasticity. We show here that positive correlation between pre- and postsynaptic activity induced LTP and facilitated dendritic integration (E–S potentiation) in CA1 pyramidal neurons whereas negative correlation induced LTD and depressed dendritic integration (E–S depression). These changes in dendritic integration required NMDA receptor activation and are input specific. Our data demonstrate that STDP is a common learning rule for both synaptic plasticity and plasticity of dendritic integration. Thus, the synergistic modifications in dendritic integration observed after LTP or LTD induction might represent a mechanism of functional redundancy that insures significant changes in the neuronal output when synaptic plasticity is induced.

Some of these results have been published previously in abstract form (Campanac & Debanne, 2006).

Methods

Slice preparation and electrophysiology

The methods have been detailed previously (Daoudal *et al.* 2002). Hippocampal slices (350–400 μm) were prepared from postnatal day 15–20 Wistar rats. All experiments were carried out according to the European and institutional guidelines for the care and use of laboratory animals (Council Directive 86/609/EEC and French National Research Council). Rats were deeply anaesthetized with chloral hydrate (intraperitoneal, 200 mg kg^{-1}) and killed by decapitation. Slices were cut in a sodium-free solution (mM: sucrose, 280; $NaHCO_3$, 26; D-glucose, 10; KCl, 1.3; $CaCl_2$, 1; $MgCl_2$, 10). The slices were maintained for 1 h at room temperature in oxygenated (95% O_2–5% CO_2) artificial cerebrospinal fluid (ACSF; (mM): NaCl, 125; KCl, 2.5; NaH_2PO_4, 0.8; $NaHCO_3$, 26; $CaCl_2$, 3; $MgCl_2$, 2; D-glucose, 10). Each slice was transferred to a temperature-controlled (29°C) recording chamber with oxygenated ACSF. Neurons were visualized in DIC infrared (IR)-videomicroscopy for patch-clamp experiments. In all experiments, the $GABA_A$ receptor channel blocker picrotoxin (PiTX, 100 μM) was applied. The area CA1 was surgically isolated to prevent epileptiform bursting. Whole-cell patch-clamp recordings were obtained from CA1 pyramidal cells. The electrodes were filled with an internal solution containing (mM): potassium gluconate, 120; KCl, 20; Hepes, 10; EGTA, 0.5; $MgCl_26H_2O$, 2; Na_2ATP, 2. Glass stimulating electrodes filled with extracellular saline were placed in the stratum radiatum. In control and test conditions, EPSPs were evoked at 0.1 Hz. The stimulus intensity (80–180 μs, 40–100 μA) was adjusted to evoke EPSPs that elicited postsynaptic spikes in ∼30% of cases. LTP and LTD were induced by the repetitive association of an EPSP and a postsynaptic spike (at 0.33 Hz). The EPSP was generated by extracellular stimulation of the Schaffer collaterals and the spike by the injection of a positive step of current (300–800 pA, 3–5 ms). The temporal relation between the EPSP and the spike (Δt, measured between the onset of the EPSP and the peak of the spike) determined the sign of the synaptic plasticity. Positive pairing (Δt: +5/+50 ms, 100 repetitions) induced LTP, whereas negative pairing (Δt: −5/−50 ms, 150 repetitions) induced LTD. The number of repetitions was not equal because LTD usually requires a large number of stimulations to produce a sustained and moderate elevation in postsynaptic calcium concentration whereas LTP can be induced with a limited number of stimulations that cause a brief and nearly maximal postsynaptic calcium elevation. The test of E–S coupling during pre- and postconditioning periods corresponds to the positive correlation protocol ($\Delta t = 13 \pm 1$ ms, $n = 13$). However, the number of supra-threshold EPSPs during the control period (20 ± 3 for positive correlation experiments and 24 ± 4 for negative correlation experiments) was not sufficient to produce a significant change in synaptic transmission. We show that 25 positive pairings with a delay of 13 ms between the EPSP and the postsynaptic spike did not significantly affect the EPSP slope (see online Supplemental Fig. 1).

Drugs were bath applied. PiTX, 4-AP (4-aminopyridine), riluzole, CsCl and D-AP5 (D-(−)-2-amino-5-phosphonopentanoic acid) were purchased from Sigma and ZD-7288 was obtained from Tocris. Riluzole (6 μM) reduced postsynaptic firing, confirming its action on sodium channels (Urbani & Belluzzi, 2000). ZD-7288 has been shown to have presynaptic effects at concentrations greater than 10 μM (Chevaleyre & Castillo, 2002). The low concentration used here (1 μM) did not affect the synaptic strength but efficiently blocked postsynaptic I_h indicating that ZD-7288 had no major presynaptic effect in our experiments. In addition to its major effect on I_h, Cs^+ also

blocks inward rectifier K^+ (Kir) currents (Thompson *et al.* 2000). However, the effects of Cs^+ or ZD were comparable and could be perfectly mimicked by local reduction in the h-conductance (E. Campanac, N. Ankri & D. Debanne, unpublished observations). Furthermore, Kir2.1 channels are only weakly expressed in CA1 neurons (Prüss *et al.* 2005). 4-AP is not specific to the A-type K^+ current (Storm, 1988) but it effectively blocks the transient A-current in CA1 pyramidal neurons and enhances EPSP amplitude (Hoffman *et al.* 1997).

Data acquisition and analysis

Electrophysiological recordings were obtained using an Axoclamp 2B amplifier, Acquis1 software (Bio-Logic, Orsay, France) or pCLAMP version 8 and 9. Data were analysed with IGOR version 5.03 (WaveMetrics, Lake Oswego, OR, USA). Pooled data are presented as either mean ± S.E.M. or box plots and statistical analysis was performed using the Mann–Whitney *U* test or the paired *t* test of Student.

E–S coupling was represented by the firing probability as a function of the EPSP slope. EPSP slopes measured during the first 2 ms were sorted in 0.2–0.5 mV ms^{-1} bins. The firing probability was determined for each bin. Changes in E–S coupling were quantified by expressing the mean firing probability after pairing as a percentage of the mean firing probability in the control period. In two neurons, the mean firing probability was 0 before pairing, thus E–S coupling in these cells was arbitrarily set to the mean E–S potentiation (194%) calculated from the other data points. To confirm this analysis, the E–S shift for a firing probability of 50% has also been analysed (Staff & Spruston, 2003). Since the intensity was kept constant during the experiment, the E–S curves were not always complete. Therefore the number of cells where the E–S shift could be measured was slightly reduced.

The amplitude/slope (*A*/Slp) relation of the EPSP was studied to assess the change in EPSP amplification. To quantify the change in *A*/Slp, EPSP slopes were sorted in 0.2–0.5 mV ms^{-1} bins and the mean EPSP amplitude was calculated for each bin. The change value of each cell was obtained by averaging the normalized EPSP amplitude corresponding to each class of EPSP slope. A linear fit was performed for each group of data to facilitate the estimation of the *A*/Slp change in the figures. The spike threshold was determined as the voltage corresponding to the time where the derivative exceeded 10 mV ms^{-1}.

Results

Bidirectional long-term plasticity of E–S coupling associated with STDP

All the experiments were performed in the presence of 100 μM PiTX to block $GABA_A$ receptor-mediated inhibition. To avoid epileptiform activity, the CA1 region was surgically isolated. Stable whole-cell patch-clamp recordings were obtained from CA1 pyramidal neurons. Positive pairing with short delays ($+5 < \Delta t < +50$ ms) induced a stable potentiation of the EPSP slope (Fig. 1*A*; $129 \pm 6\%$ of the control, $n = 29$). Dendritic integration was evaluated before and after pairing by plotting the probability of spiking *versus* EPSP slope. After positive pairing, the EPSP–spike (E–S) curve was shifted towards the left and the firing probability was increased for a given EPSP slope, attesting to E–S potentiation (Fig. 1*B*). On average, the E–S potentiation was $194 \pm 21\%$ of the control; $n = 11$) and the mean E–S shift was -0.23 ± 0.06 mV ms^{-1} ($n = 10$). No change in the input resistance tested with a brief hyperpolarizing pulse (50 ms; −20 pA) was observed after the induction of LTP and E–S potentiation (Fig. 1*A*; $101 \pm 1\%$, $n = 29$).

Negative pairing with a delay between −50 and −5 ms (150 repetitions) induced LTD (Fig. 1*C*; $82 \pm 3\%$, $n = 25$) and decreased E–S coupling (Fig. 1*D*). After negative pairing, E–S coupling was $71 \pm 14\%$ ($n = 14$) of the control and the mean E–S shift was $+0.11 \pm 0.01$ mV ms^{-1} ($n = 9$). These changes were significantly different from those obtained after short positive correlation (Mann–Whitney *U* test: EPSP slope, $P < 0.01$; E–S coupling, $P < 0.001$; and E–S shift, $P < 0.01$). No change in the input resistance was observed after the induction of LTD and E–S depression (Fig. 1*C*; $101 \pm 1\%$, Mann–Whitney *U* test, $P > 0.1$, $n = 25$). Our results indicate that E–S plasticity is induced in parallel and in synergy with synaptic plasticity.

Temporal dependence of long-term plasticity of E–S coupling

Synaptic plasticity precisely depends on the timing between pre- and postsynaptic activities and synaptic efficacy is not affected for long positive or negative intervals (Debanne *et al.* 1998; Bi & Poo, 1998; Feldman, 2000). We have therefore examined whether E–S coupling was affected by pairing protocols with long positive or negative delays ($> \pm 50$ ms). We observed that positive correlation with long delay ($\Delta t > +50$ ms) failed to induce LTP ($106 \pm 4\%$, $n = 4$; Fig. 2*A*) and did not affect E–S coupling ($105 \pm 6\%$ of the control; $n = 3$; Fig. 2*B*). Neither LTD ($101 \pm 3\%$, $n = 8$; Fig. 2*C*) nor E–S depression ($111 \pm 9\%$ of the control E–S coupling, $n = 4$; Fig. 2*D*) were observed with a delay greater than −50 ms. In contrast with short delays, there was no differential changes for long positive or long negative intervals (Mann–Whitney *U* test: EPSP slope, $P > 0.5$ and E–S coupling, $P > 0.5$). Most importantly, the time-windows for synaptic and E–S plasticity were virtually identical (Fig. 3*A* and *B*). Moreover, E–S

potentiation was found to occur when the EPSP was potentiated whereas E–S depression was concomitant with synaptic depression (Fig. 3*C*), indicating that both types of plasticity are functionally synergistic. We conclude that E–S plasticity in CA1 pyramidal neurons follows the STDP rule initially established for synaptic transmission.

E–S plasticity associated with STDP requires NMDA receptor activation

In the CA1 region of the hippocampus, E–S potentiation and depression require NMDA receptor activation (Daoudal *et al.* 2002). We therefore tested whether long-term plasticity of E–S coupling induced by STDP protocols also depended upon activation of these receptors. In the presence of D-AP5 (50 μM), positive correlation of pre- and postsynaptic activity failed to induce LTP ($94 \pm 2\%$, $n = 5$) and E–S potentiation ($77 \pm 14\%$ of the control coupling, Fig. 4*A*). Similarly, NMDA receptor activation was necessary for inducting long-term E–S depression with negative pairings. In the presence of 50 μM D-AP5, neither LTD ($98 \pm 3\%$, $n = 11$), nor E–S depression were observed ($117 \pm 14\%$ of the control E–S coupling, Fig. 4*B*). These results are

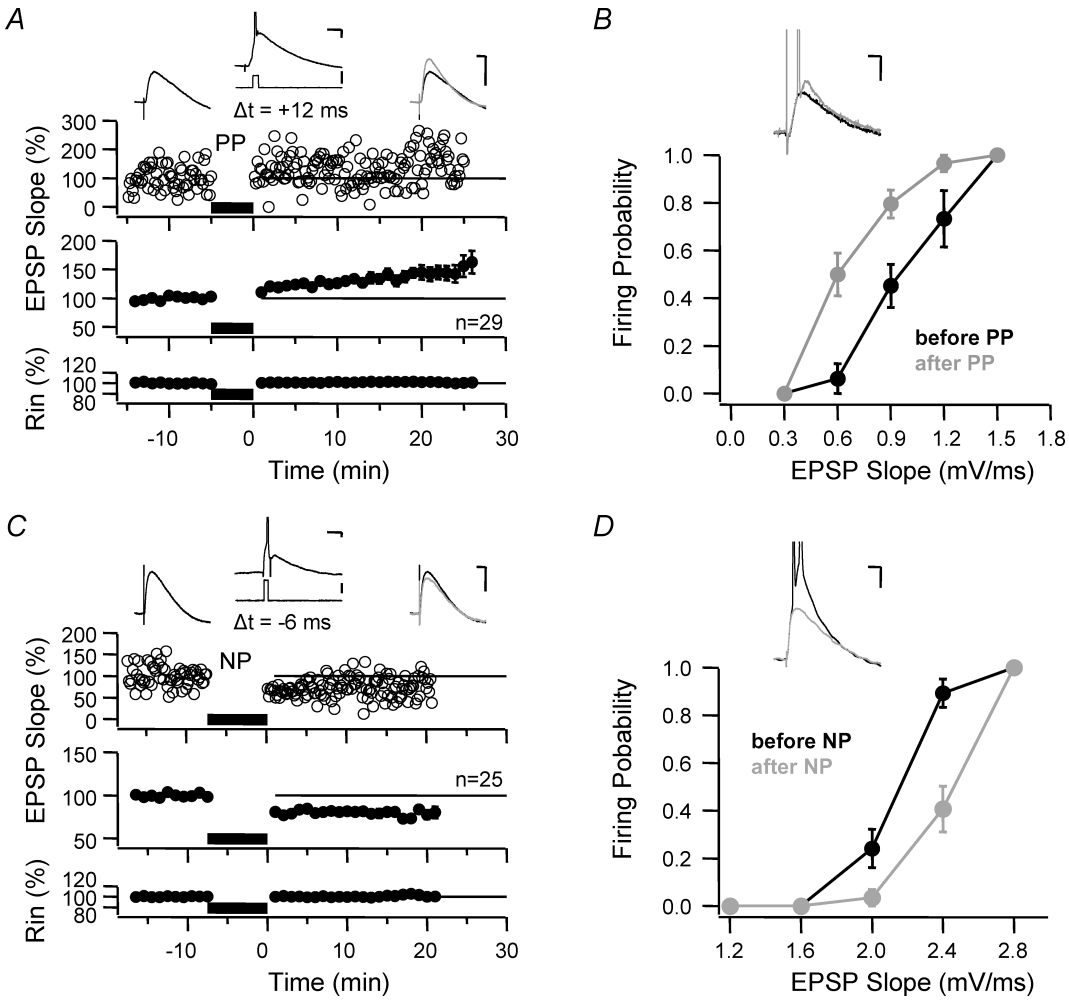

Figure 1. Bi-directional plasticity of dendritic integration associated with spike timing-dependent synaptic plasticity
A, induction of LTP with short positive pairing (PP, inset). Upper graph, time-course of the EPSP slope measured on individual responses in a single experiment (delay: +12 ms). Middle graph, EPSP slope pooled over 29 experiments. Lower graph, normalized input resistance (Rin) pooled over 29 experiments. *B*, facilitation in dendritic integration following induction of LTP with a short PP (delay: +12 ms). Plot of the firing probability as a function of EPSP slope before and after LTP induction (neuron from panel *A*). Error bars correspond to S.E.M. E–S shift is −0.38 mV ms^{-1}. *C*, induction of LTD with short negative pairing (NP, inset). The general organization is similar to *A* (upper graph, single experiment, middle and lower graphs time-courses of EPSP slope and Rin over 23 experiments, respectively). *D*, depression in dendritic integration following induction of LTD with a short NP (−6 ms). Plot of the firing probability as a function of EPSP slope before and after LTD induction. Scale bars 20 ms, 5 mV, 200 pA. In this example, E–S shift was +0.31 mV ms^{-1}.

significantly different from those obtained in the absence of D-AP5 (Mann–Whitney U test, $P < 0.05$). Therefore, we conclude that long-term E–S potentiation and depression induced by STDP protocols require activation of NMDA receptors.

No change in spike threshold

In cerebellar granule cells, facilitation of EPSP–spike coupling associated with LTP results from a reduction in the spike threshold (Armano *et al.* 2000). Similarly, the increased excitability observed after STDP-induced LTP in CA1 pyramidal neurons is associated with a hyperpolarization of the spike threshold (Xu *et al.* 2005). We therefore analysed whether the threshold of the action potential (AP), defined as the voltage where dV/dt exceeded 10 mV ms^{-1}, was altered after positive or negative correlation. No differential modification in the threshold was observed when LTP or LTD was induced with short positive or negative correlation, respectively (variation in the threshold: -0.48 ± 0.23 mV $n = 7$ for +5/+50 ms *versus* -0.61 ± 0.32 $n = 11$ for −5/−50 ms, Mann–Whitney U test $P > 0.05$). Thus, changes in EPSP–spike coupling cannot be accounted for by a modification in the AP threshold measured at the cell body and other mechanisms should be envisaged.

Changes in the amplitude/slope relation of the EPSP

Alternatively, E–S changes may result from a change in EPSP amplification under the control of voltage-gated

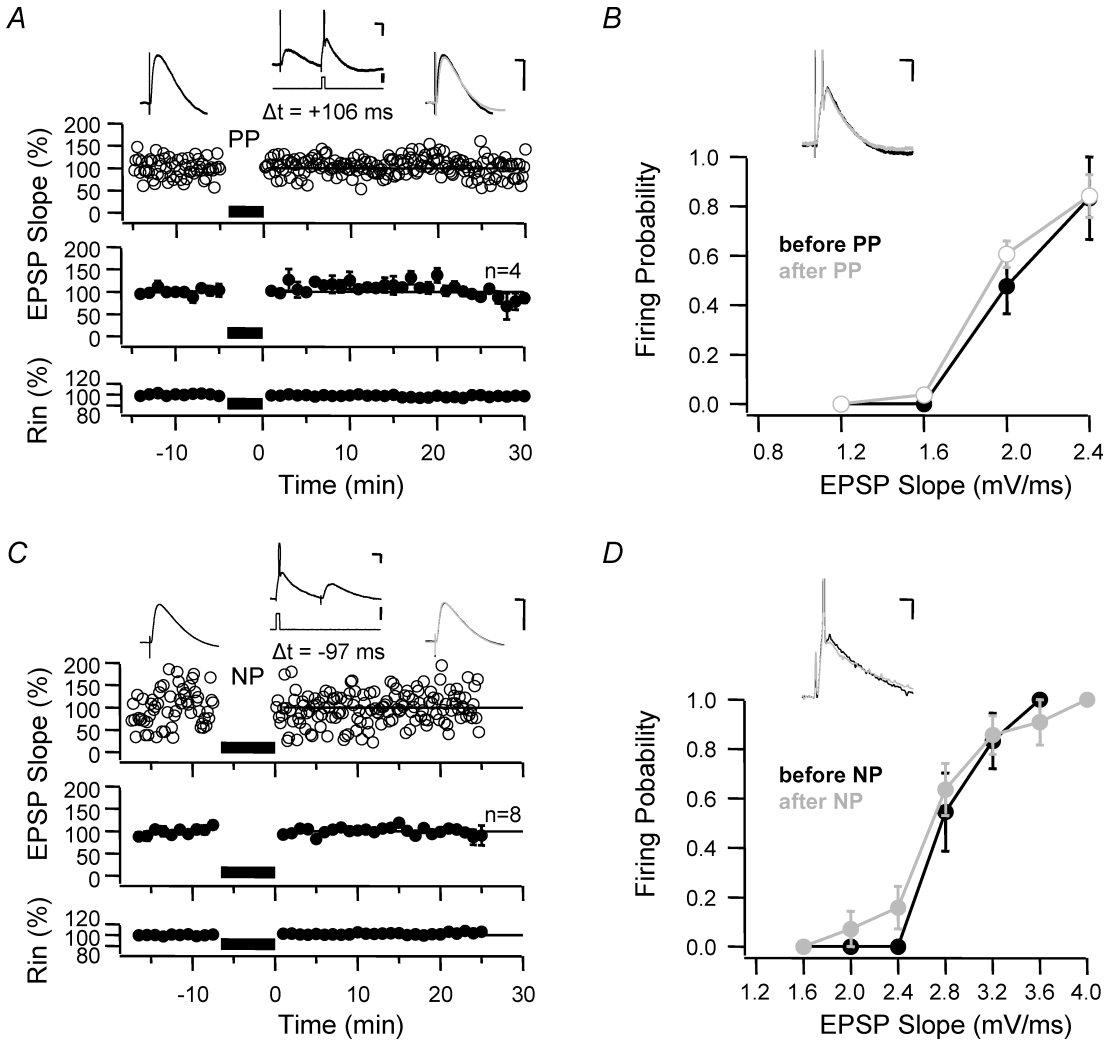

Figure 2. Temporal specificity of the plasticity of dendritic integration
Positive pairing with long delay (here +106 ms) had no effect on synaptic transmission (*A*) and dendrtic integration (*B*). E–S shift here was −0.08 mV ms^{-1}. Negative pairing with long delays (here −97 ms) had no effect on synaptic transmission (*C*) and dendritic integration (*D*). E–S shift here was −0.07 mV ms^{-1}. Scale bars 20 ms, 5 mV, 200 pA.

conductances located in the dendrites. In CA1 hippocampal neurons, hyperpolarizing-activated cationic current (I_h) and A-type K^+ current (I_A) attenuate EPSPs (Hoffman *et al.* 1997; Magee, 1998) whereas persistent sodium current (I_{NaP}) amplified EPSPs (Lipowsky *et al.* 1996). It is not yet clear how these currents determine the EPSP–spike coupling. A simple way to test their role on EPSP waveform consists in determining their action on the amplitude/slope (*A*/Slp) relation of subthreshold EPSPs (see Methods). Blockade of attenuating voltage-gated currents (with 2.5 mM external Cs^+ or 1 μM ZD-7288 for I_h or with 1 mM 4-AP for I_A) increased the *A*/Slp ratio of the EPSP (Fig. 5*A* and *B*). On average, *A*/Slp was, respectively, $107 \pm 3\%$ of the control ($P < 0.05$ paired *t* test; $n = 9$) when I_h was blocked with h-channel blockers and $128 \pm 9\%$ ($P < 0.05$ paired *t* test; $n = 6$; Fig. 5*D*) when I_A was blocked with 4-AP. Conversely, the blockade of I_{NaP} with 6 μM riluzole (Urbani & Belluzzi, 2000) reduced the *A*/Slp ratio of the EPSP (Fig. 5*C*). On average, *A*/Slp was $91 \pm 2\%$ of the control ($P < 0.05$ paired *t* test; $n = 5$; Fig. 5*D*). These results indicate that voltage-gated currents (such as I_h, I_A or I_{NaP}) regulate the A/Slp relation of the EPSP and may thus be the expression mechanism of the bi-directional plasticity of EPSP–spike coupling induced by STDP protocols.

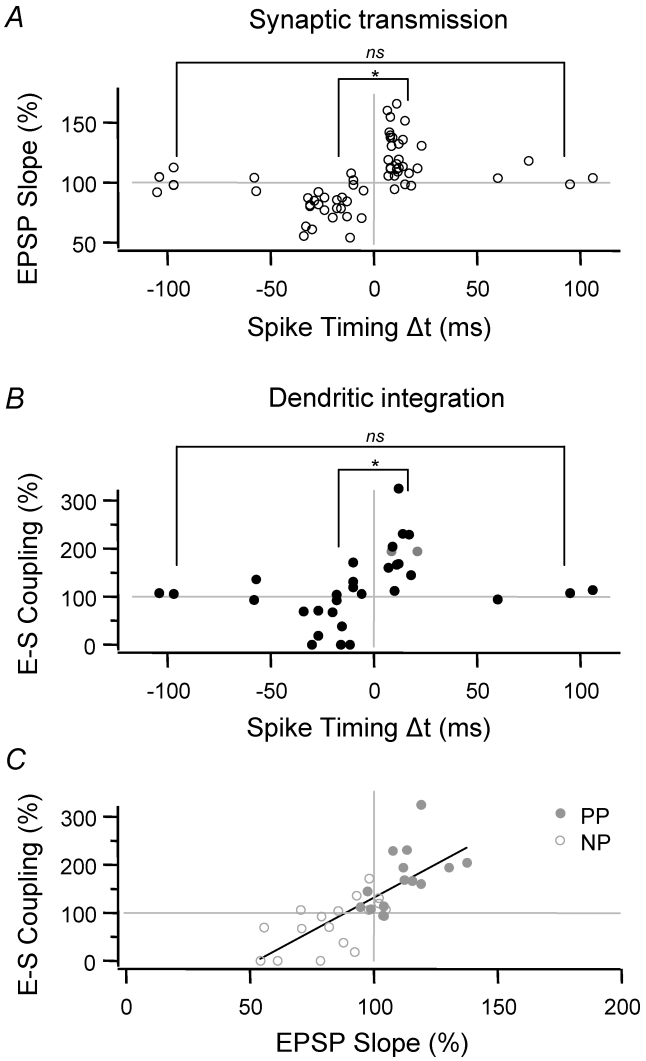

Figure 3. STDP of dendritic integration
A, plot of the normalized EPSP slope *versus* spike timing. *B*, plot of the normalized E–S coupling *versus* spike timing. Note the similarity in the profiles obtained for synaptic transmission (*A*) and dendritic integration (*B*). *C*, plot of the normalized E–S coupling *versus* EPSP slope in all experiments. Note the correlation between synaptic and non-synaptic changes (linear regression: $y = 2.8x - 145.2$, $R^2 = 0.58$).

To test this hypothesis, we examined the *A*/Slp relation before and after inducing STDP. The *A*/Slp relation was enhanced when LTP was induced with positive correlation (18/29; mean $= 104 \pm 1\%$, $n = 29$) but reduced when LTD was induced with negative correlation (22/25; mean $= 91 \pm 1\%$, $n = 25$). It was differentially affected after short positive or negative pairing (Fig. 6*A*, *B* and *E*; Mann–Whitney *U* test, $P < 0.001$) but not following long positive or negative pairing (Fig. 6*C*, *D* and *E*; Mann–Whitney *U* test, $P > 0.5$). These data indicate that the EPSP–spike plasticity observed following STDP may result from the long-term regulation of the conductances controlling EPSP amplification. In addition, changes in EPSP–spike coupling may be the consequence of the regulation of the *A*/Slp relation by these voltage-gated conductances. E–S potentiation observed after LTP could simply result from the increase in *A*/Slp whereas E–S depression observed after LTD may result from a decrease in *A*/Slp.

Long-term plasticity of dendritic integration associated with STDP is input specific

The spatial restriction of activity-dependent synaptic plasticity is thought to preserve a high potential for information storage. This level of functional and spatial resolution would be dramatically reduced if the plasticity of dendritic integration was generalized to other synaptic inputs. Input specificity has been demonstrated for long-term facilitation in dendritic integration associated with LTP and LTD induced by patterned presynaptic stimulation (Daoudal *et al.* 2002). However, it is not yet clear whether long-term changes in dendritic integration induced with STDP protocol are also restricted to the conditioned pathway. To address this question, the *A*/Slp relation of the EPSP was monitored at two independent synaptic pathways before and after positive or negative correlation. One pathway located at $\sim$100 μm from the pyramidal cell layer was paired with a postsynaptic spike procedure whereas the second pathway located at $\sim$40 μm from the cell body layer was stimulated as in control conditions (0.1 Hz). After positive correlation,

the paired pathway was potentiated (normalized EPSP slope: 145 ± 5%, $n = 4$) but the control pathway remained unchanged (97 ± 4% of the control, $n = 4$; paired t test $P < 0.05$; Fig. 7). Most importantly, the A/Slp ratio was differentially increased at the paired pathway (109 ± 4% of the control, $n = 4$) but not at the control pathway (99 ± 4%, $n = 4$; paired t test, $P < 0.05$), suggesting that the facilitation in dendritic integration is specific to the positively paired pathway. Thus, these results indicate that there are local input-dependent changes in EPSP amplification, presumably in the dendrites.

Similar differential changes were observed with negative correlation. LTD was induced at the paired but not at the control pathway (normalized EPSP slope; 79 ± 4% *versus* 115 ± 10%, $n = 6$, paired t test $P < 0.05$, Fig. 8). The A/Slp ratio was differentially decreased at the conditioned and at the control pathway (90 ± 3% *versus* 106 ± 4% $n = 6$, paired t test $P < 0.05$). We conclude that long-term plasticity of dendritic integration induced in parallel with STDP protocols is input specific and thus respects the spatial selectivity of synaptic changes.

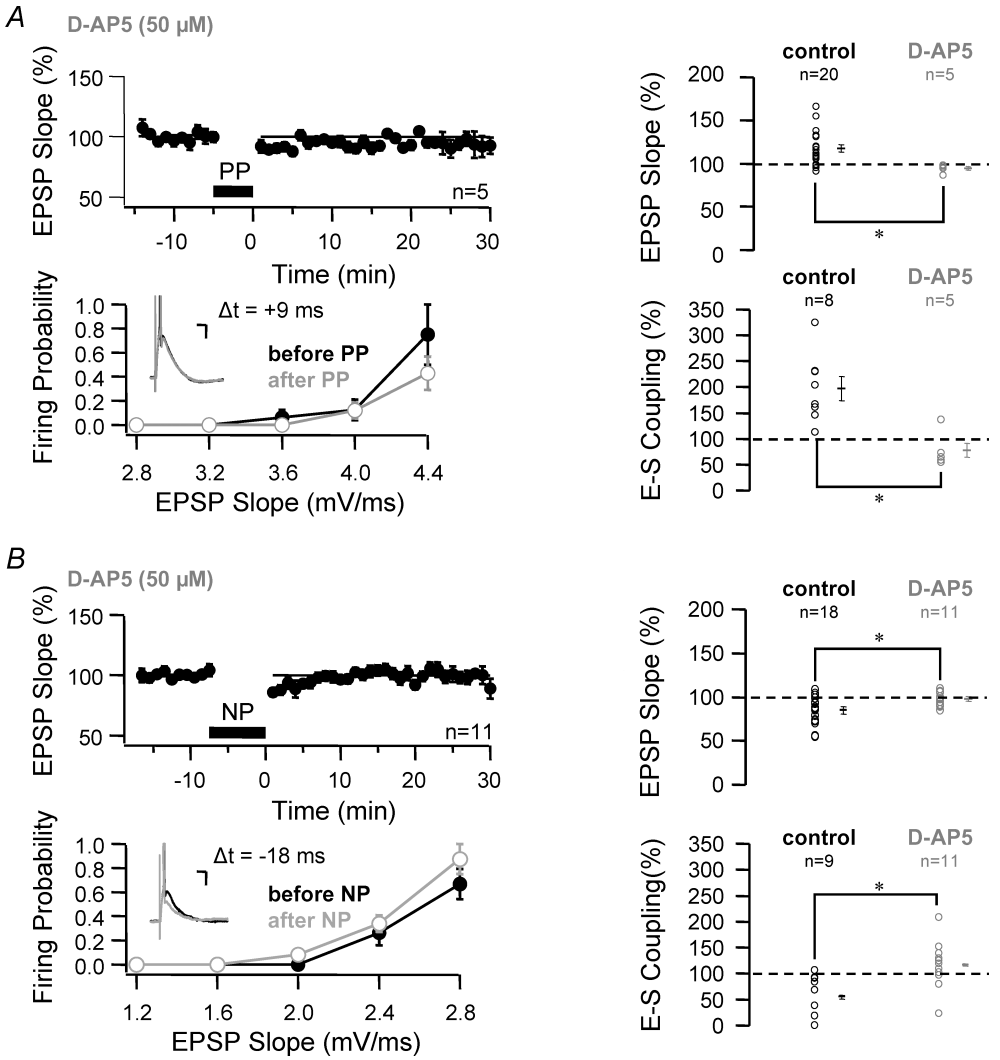

Figure 4. Bidirectional plasticity of dendritic integration requires activation of NMDA receptors
A, in the presence of 50 μM D-AP5, positive pairing (PP) with a short delay (< 50 ms) failed to produce LTP and facilitation in dendritic integration. Upper left graph, normalized EPSP slope pooled over 5 experiments. Lower left graph, firing probability plots in a representative experiment before and after LTP induction. Right, normalized changes in EPSP slope (top) and EPSP–spike coupling (bottom) after PP in control conditions and in the presence of D-AP5. *B*, in the presence of 50 μM D-AP5, negative pairing (NP) with a short delay (<−50 ms) failed to induce LTD and depression in dendritic integration. Right, normalized changes in EPSP slope (top) and EPSP–spike coupling (bottom) after NP in control conditions and in the presence of D-AP5. Scale bars 20 ms, 5 mV.

Discussion

We show that the STDP rule initially established for long-term synaptic plasticity is also valid for the plasticity of dendritic integration in CA1 pyramidal neurons. The generation of a postsynaptic spike by the conditioned synaptic pathway was facilitated following induction of LTP with short positive correlation ($\Delta t < +50$ ms) but decreased after LTD induction with short negative correlation ($\Delta t < -50$ ms). Thus, the observed plasticity of dendritic integration represents a mechanism of functional redundancy that ensures significant changes in the neuron output when synaptic plasticity is induced. The temporal selectivity of the effect was demonstrated by the lack of changes in both synaptic transmission and dendritic integration for long positive or negative correlation ($> \pm 50$ ms). Plasticity of dendritic integration required activation of NMDA receptors, indicating that the plasticity of dendritic integration and synaptic plasticity share common induction pathways. Synaptic and E–S changes were found to be correlated, suggesting that both the synaptic strength and the input–output function of the neuron changed synergistically at the postsynaptic side. All these changes were observed in the presence of a blocker of $GABA_A$ receptors indicating that these modifications do not result from changes in the balance between synaptic excitation and inhibition but rather from a modification in the activity of voltage-gated channels that shape EPSPs. This conclusion is supported by the fact that the EPSP amplification evaluated by the *A*/Slp relation was differentially affected following induction of spike timing-dependent synaptic plasticity. For a given slope the EPSP amplitude was, respectively, increased or decreased when LTP or LTD was induced. These modifications are likely to facilitate spike generation after LTP or conversely decrease spike generation after LTD. Importantly, these modifications were found to be specific to the conditioning input. Similar modifications in the *A*/Slp ratio of the EPSP could be mimicked by bath application of blockers of EPSP amplification or EPSP attenuation, suggesting that changes in dendritic integration might be mediated by the regulation of intrinsic voltage-gated conductances.

Synaptic plasticity induced by STDP with single spikes

Our results show that LTP or LTD could be consistently induced in the presence of the $GABA_A$ receptor antagonist PiTX when the test EPSP was positively or negatively paired with single postsynaptic spikes, respectively. Although induction of LTD with single postsynaptic spikes is a robust

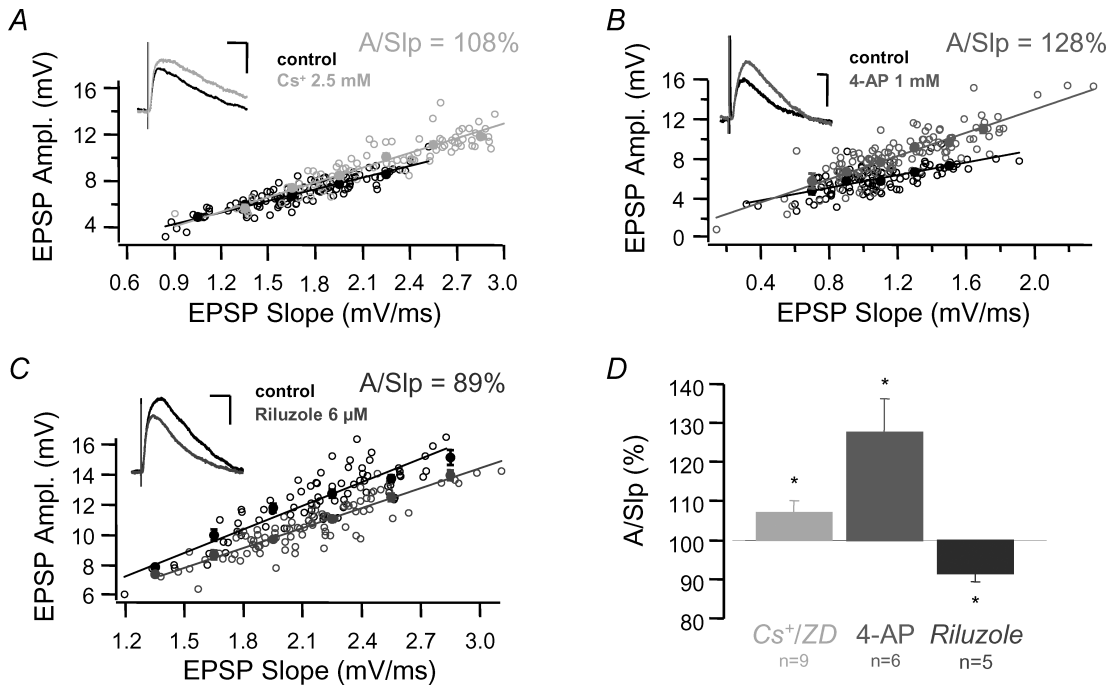

Figure 5. Voltage-gated currents determine the amplitude/slope (*A*/Slp) relation of the EPSP
In control conditions (open black symbols), this relation can be fitted by a linear regression. *A*, in the presence of an h-channel blocker (here external Cs^+) the amplitude of the EPSP is slightly increased for a given EPSP slope (see inset). Averaged amplitudes in each class of EPSP slope are illustrated by filled symbols. *B*, in the presence of an A-type K^+ blocker (4-amino-pyridine, 1 mM) the EPSP amplitude is also increased. *C*, in the presence of the persistent sodium channel blocker riluzole (6 μM) it is, however, decreased. *D*, summary of the changes in *A*/Slp relation of the EPSP induced by blockers of I_h (Cs^+ and ZD), I_A (4-AP) and I_{NaP} (riluzole). Scale bars 20 ms, 5 mV.

phenomenon, induction of LTP is a matter of controversy. Induction of LTP using single postsynaptic spikes was initially reported in organotypic (Debanne *et al.* 1998) and dissociated hippocampal cultures (Bi & Poo, 1998). These findings were questioned by subsequent studies in acute slices showing that LTP was consistently induced in CA1 neurons when EPSPs were paired with bursts of two to three action potentials but not with single spikes (Pike *et al.* 1999; Wittenberg & Wang, 2006). Development of GABAergic synaptic inhibition represents a major gating mechanism for induction of LTP and may account for this discrepancy. In fact, LTP is consistently induced with single postsynaptic spikes in young rats (< P15) but not in old rats (> P20) (Meredith *et al.* 2003). In mature animals, robust LTP is induced with single postsynaptic spikes when $GABA_A$ receptors are blocked with PiTX. Our data therefore confirm these results. The control of LTP by synaptic inhibition may result from the interference of inhibitory synaptic potentials with NMDA receptor activation and/or with back-propagated action potentials (reviewed in Sourdet & Debanne, 1999).

STDP is a learning rule for synaptic and non-synaptic plasticity

Our study supports the conclusion that the learning rules established for synaptic transmission may also be valid for intrinsic plasticity. We previously showed that the BCM rule not only describes synaptic changes but also E–S

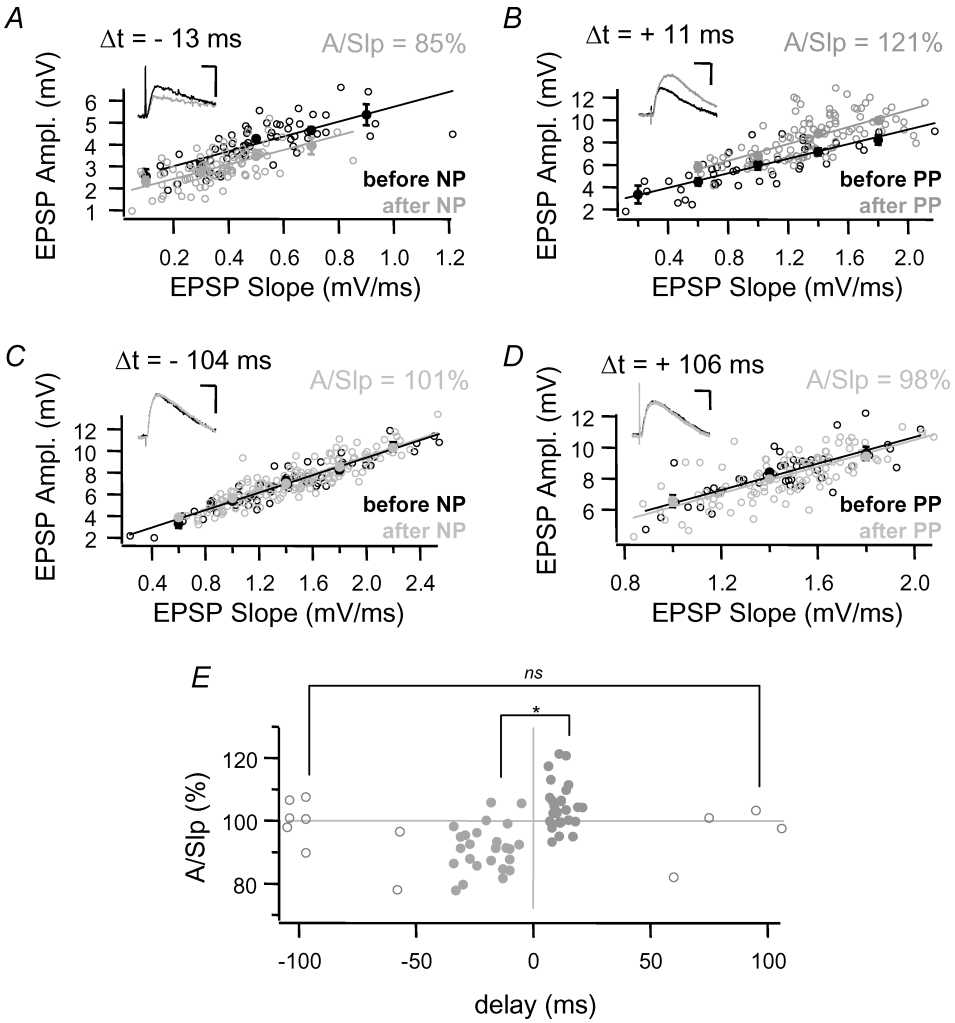

Figure 6. Changes in the *A*/Slp relation of the EPSP after STDP
A, effect of short negative pairing (delay −13 ms) on the *A*/Slp relation. *B*, effect of short positive pairing (delay +11 ms) on the *A*/Slp relation. *C* and *D*, effects of long negative (*C*) and positive (*D*) pairing (−104 and +106 ms, respectively) on the *A*/Slp relation. *E*, normalized *A*/Slp *versus* spike timing. Note the loss of *A*/Slp for short negative delays and the gain in *A*/Slp for short positive delays ($P < 0.05$). For long positive or negative delays (○) the changes were not significant. Scale bars 20 ms, 5 mV.

plasticity in CA1 pyramidal neurons (Daoudal *et al.* 2002; Daoudal & Debanne, 2003*a*). The present study generalizes this statement to the second major learning rule, the STDP rule, and strengthens the evidence for the essential similarity of the two rules (Karmakar & Buonomano, 2002; Shouval *et al.* 2002).

Postsynaptic changes in EPSP summation have been reported in CA1 pyramidal neurons following a STDP protocol (Wang *et al.* 2003). These changes were synergistic with synaptic plasticity but the temporal specificity was not tested. Our results demonstrate that STDP represents a common learning rule for synaptic plasticity and plasticity of dendritic integration at the postsynaptic side of CA1 pyramidal neurons. More specifically, our study shows that the STDP rule is not only valid for E–S coupling (Fig. 3) but also for EPSP amplification (Fig. 6). EPSP amplification was facilitated following induction of LTP by positive correlation but depressed when LTD was induced with negative correlation. Thus, plasticity induced by the precise temporal relationship between pre- and postsynaptic activity not only affects the excitatory postsynaptic current but also determined voltage-gated mechanisms controlling EPSP amplification in a functionally synergistic way.

A functional synergy between synaptic changes and plasticity of presynaptic intrinsic excitability has been also reported in central neurons. In synaptically connected hippocampal and neocortical neurons, positive or negative correlation not only affects synaptic efficacy but also increases or decreases the global excitability of the presynaptic neuron, respectively (Ganguly *et al.* 2000; Li *et al.* 2004). Thus, long-term pre- and postsynaptic changes in neuronal excitability are induced in parallel and in synergy with long-term synaptic plasticity (Campanac & Debanne, 2007). In conclusion, plasticity of intrinsic excitability should be incorporated into a general framework in which synaptic and non-synaptic plasticity interact coherently and harmoniously (Daoudal & Debanne, 2003*a*; Campanac & Debanne, 2007).

In vivo, CA3 and CA1 neurons fire not only single spikes but also bursts of spikes. The protocols used here could be closer to physiological patterns of activity; however,

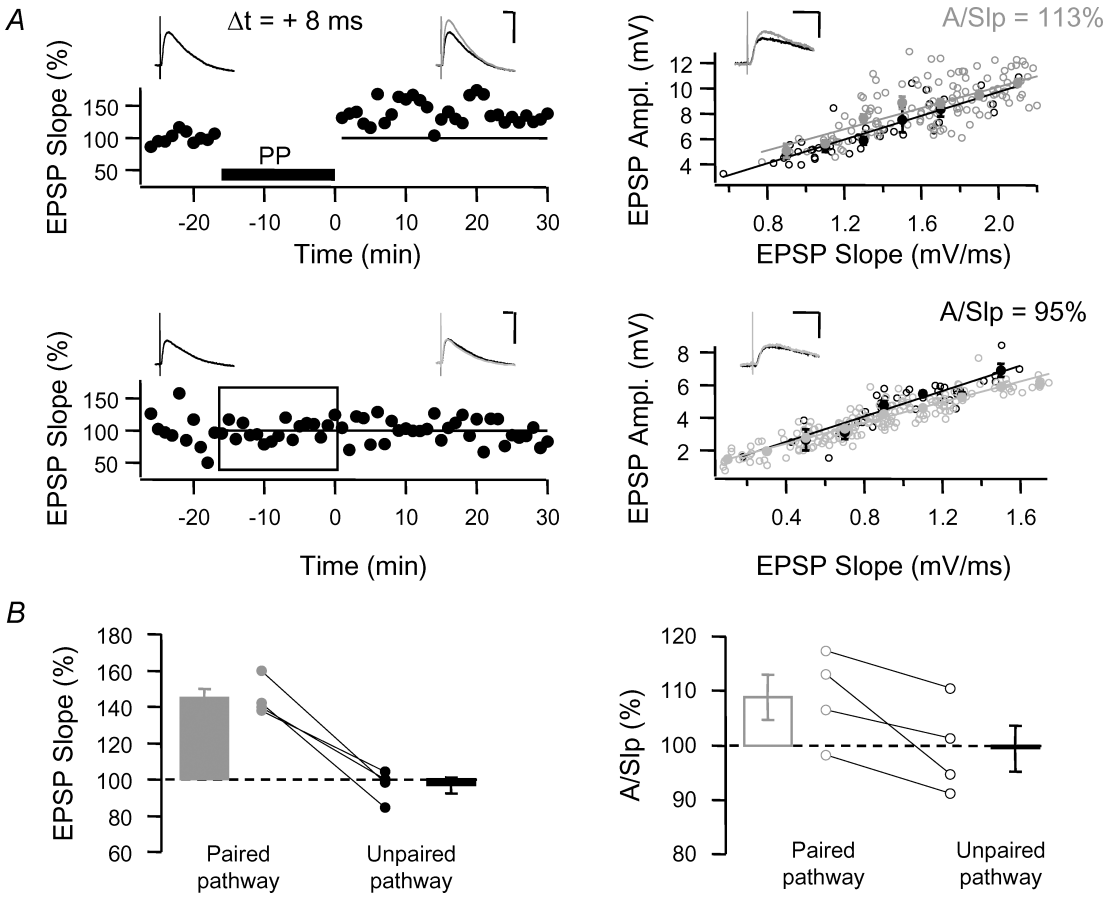

Figure 7. Input-specific facilitation in dendritic integration
A, single experiment. Left, time-courses of the EPSP slope (1 min averages) for the paired (top) and unpaired (bottom) pathways. Right, *A*/Slp relation for the paired (top) and unpaired (bottom) pathways. *B*, normalized EPSP slope (left) and normalized *A*/Slp relation of the EPSP (right). Scale bars 20 ms, 5 mV.

the parameters are controlled and these protocols provide very simple and reproducible results. It will be important to define in the future the rules governing E–S plasticity with more realistic patterns of activity including multiple temporal spike interaction (Paulsen & Sejnowski, 2000; Sjöström *et al.* 2001; Froemke & Dan, 2002; Wang *et al.* 2005).

Long-term regulation of EPSP amplification, a mechanism for E–S plasticity

E–S potentiation and E–S depression are partly mediated by an imbalance between synaptic excitation and GABAergic inhibition (Hess & Gustafsson, 1990; Jester *et al.* 1995; Daoudal *et al.* 2002; Staff & Spruston, 2003; review in Daoudal & Debanne, 2003*a*). All the experiments reported here were performed in the presence of the $GABA_A$ receptor blocker PiTX. Although our study addressed the mechanisms underlying $GABA_A$ receptor-independent E–S plasticity, it does not preclude the existence of a GABAergic component in E–S plasticity induced by STDP protocols (see Marder & Buonomano, 2004).

The bidirectional changes in EPSP–spike coupling were not associated with a modification in the spike threshold. This finding is apparently in discrepancy with the study by Xu *et al.* (2005) where a hyperpolarization of 10 mV was reported after LTP induction. However, the hyperpolarization of the spike threshold may result from the elevated postsynaptic spiking during the induction protocol (400 spikes at 20 Hz in their study *versus* 100 spikes at 0.3 Hz in ours). In fact, postsynaptic firing at 30–40 Hz is sufficient to increase intrinsic excitability in L5 cortical neurons by a reduction in the spike threshold (Cudmore & Turrigiano, 2004). Thus, the lack of hyperpolarization of the spike threshold may well result from the fact that postsynaptic spiking was moderate in our experiments. Rather, EPSP amplification was bi-directionally regulated following LTP or LTD induced with spike timing-dependent protocols. Changes in field EPSP waveform have been reported following induction of LTP (Hess & Gustafsson, 1990) but our

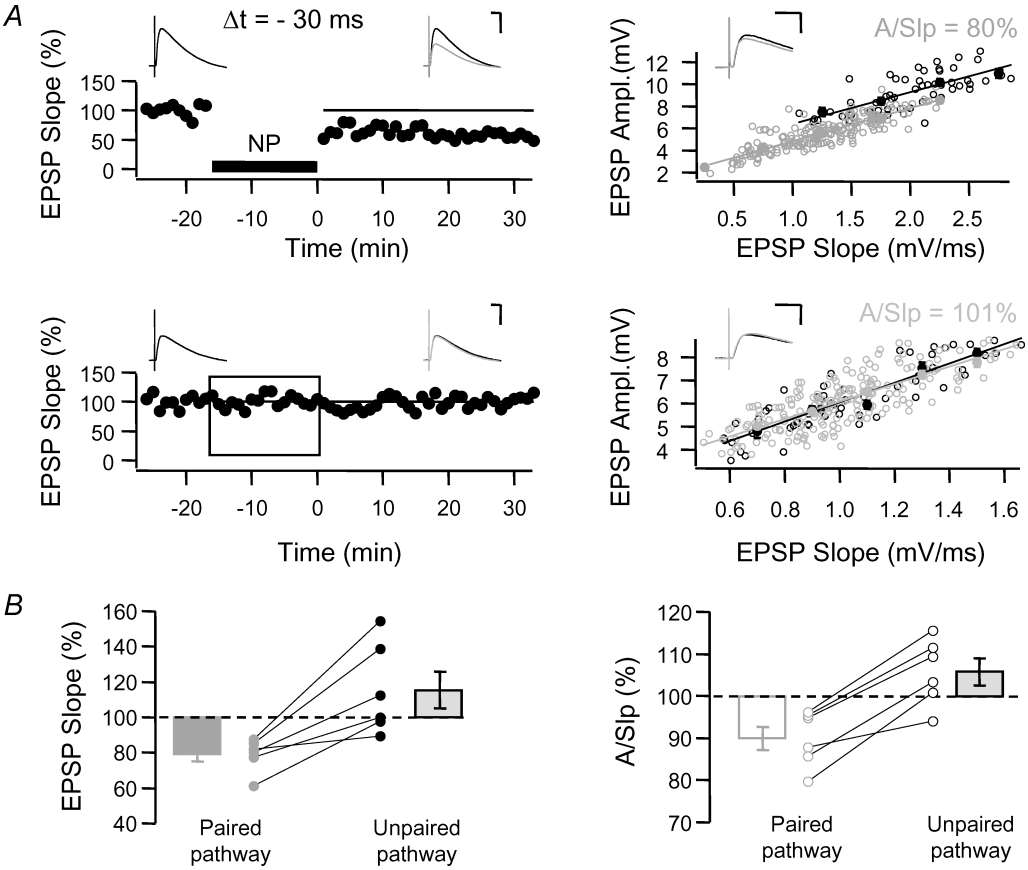

Figure 8. Input-specific depression in dendritic integration
A, single experiment. Left, time-courses of the EPSP slope (1 min averages) for the paired (top) and unpaired (bottom) pathways. Right, *A*/Slp relation for the paired (top) and unpaired (bottom) pathways. *B*, normalized EPSP slope (left) and normalized *A*/Slp relation of the EPSP (right). Scale bars 20 ms, 5 mV.

study constitutes the first report to our knowledge of a bidirectional long-term plasticity of EPSP amplification. These modifications could well account for the change in EPSP–spike coupling induced by STDP since the EPSP amplitude for a given slope was, respectively, enhanced after positive correlation or depressed after negative correlation.

These changes are unlikely to be mediated by a synaptic component. In principle, a change in EPSP waveform after LTP could result from a modification in synaptic inhibition, in the recruitment of polysynaptic circuits, in the kinetics of AMPA receptor-mediated EPSC or in the NMDA receptor-mediated component that controls EPSP amplitude. $GABA_A$ receptors were blocked with PiTX, thus eliminating the first possibility. Furthermore, the change in EPSP waveform is unlikely to be the result of the recruitment of polysynaptic pathways since the CA1 region was surgically isolated from the CA3 area and the subiculum, and the onset of EPSPs was always monotonic. In addition, the waveform of the AMPA receptor-mediated synaptic current remains unchanged following induction of LTP (Benke *et al.* 1998; Rammes *et al.* 1999) or LTD (Lüthi *et al.* 2004) in CA1 pyramidal neurons. Thus, the last possibility for a synaptic origin in the change in *A*/Slp involves the NMDA receptor-mediated component (Wang *et al.* 2003). However, this possibility is again unlikely since it is now well established that the AMPA/NMDA ratio at the Schaffer collateral–CA1 cell synapse is increased after induction of LTP (Isaac *et al.* 1995; Liao *et al.* 1995) and decreased after LTD (Beattie *et al.* 2000; review in Carroll *et al.* 2001). Therefore, EPSPs with similar initial slopes (i.e. similar AMPA components) would have a relatively reduced NMDA component after LTP and a relatively increased NMDA component after LTD. Supporting this view, synaptically triggered APs begin as a depolarizing ramp that is highly sensitive to QX314 but not to D-AP5 (Hu *et al.* 1992). In conclusion, the changes in EPSP amplification are unlikely to be mediated by a change in the NMDA receptor-mediated component but rather by a modification in the voltage-dependent conductances. This last hypothesis is strongly supported by the fact that the pharmacological blockade of I_h with Cs^+ or ZD-7288 and I_A with 4-AP increased the *A*/Slp relation of the EPSP whereas the blockade of I_{NaP} with riluzole had the opposite effect. EPSP amplification after LTP might result either from a decrease in I_A (Frick *et al.* 2004; Kim *et al.* 2007), in I_h (Daoudal & Debanne, 2003*b*; E. Campanac, G. Daoudal, N. Ankri & D. Debanne, unpublished observation) or an increase in sodium channel activity (Xu *et al.* 2005). Conversely, EPSP attenuation observed after LTD might result from regulation of one or more of these currents in the opposite direction. The identification of the expression mechanisms underlying E–S depression will be the purpose of another study.

Local changes in dendritic integration

Our results indicate that postsynaptic changes in dendritic integration are not global in CA1 pyramidal neurons. Both STDP-induced facilitation and depression of dendritic integration were found to be input specific, indicating that these changes are spatially restricted. The functional consequence of the input specificity of long-term plasticity of dendritic integration is that the storage capacity conveyed by synapses will be preserved (Zhang & Linden, 2003). In contrast to a previous study (Xu *et al.* 2005), the spike threshold measured at the cell body was not affected. Rather, the change in dendritic integration may result from a local modification in EPSP amplification. In fact, the *A*/Slp relation was differentially affected on the paired and unpaired pathways following induction of LTP or LTD. These results confirm previous findings indicating that E–S plasticity (Daoudal *et al.* 2002), EPSP summation (Wang *et al.* 2003; Xu *et al.* 2006) and dendritic excitability (Frick *et al.* 2004) induced in parallel with synaptic plasticity are spatially restricted in CA1 pyramidal neurons. However, a local change in intrinsic excitability is not a general rule since synaptic activity may also produce global changes in postsynaptic excitability in central neurons (Armano *et al.* 2000; Aizenman & Linden, 2000; Sourdet *et al.* 2003; Zhang *et al.* 2004).

How could a local change in dendritic excitability produce an input-specific modification in dendritic integration? Our experimental results are compatible with mathematical models of synaptic integration in active dendrites. Theoretical work shows that E–S potentiation simulated by adding local hot spots of depolarizing conductances in dendrites tends to be specific to the tetanized input if the untetanized contacts were electrically closer to the soma than the tetanized contacts (Wathey *et al.* 1992). In this study, specificity was also high if the tetanized and untetanized contacts were segregated to different primary dendrites. Thus, input-specific changes in dendritic integration are possible if voltage-gated activity is locally regulated in the dendrites. Further experimental studies will be required to identify the underlying conductances. All the experiments were performed with a control pathway more proximal ($\sim$40 μm) than the paired input ($\sim$100 μm). The spatial configuration of the two inputs relative to the cell body is unlikely to be the only source of input specificity since the facilitation of EPSP summation observed after LTP induction is equally observed when distal or proximal inputs are co-activated (Wang *et al.* 2003).

What is the precise degree of input specificity? This question has not yet been fully addressed for dendritic integration and would require detailed analysis with a systematic exploration of the spatial spread of potentiation and depression of dendritic integration. However, shared long-term facilitation in EPSP summation may occur between a potentiated and a control input separated by

50 μm, but not when the inputs are more distant (Wang *et al.* 2003). It will be important to test whether the basic computational unit estimated for synaptic transmission to 70 μm of dendritic length (Engert & Bonhoeffer, 1997) is maintained for plasticity of dendritic integration. Further studies will be required to address this question.

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Supplemental material

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