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"Developmental Shift From Long-term Depression to Long-term Potentiation at the Mossy Fibre Synapses in the Rat Hippocampus"

Enrico Cherubini
Scuola Internazionale Superiore di Studi Avanzati
Via Beirut 2 - 4
34014 Trieste
Italy

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Developmental Shift From Long-term Depression to Long-term Potentiation at the Mossy Fibre Synapses in the Rat Hippocampus

Tiziana Battistin and Enrico Cherubini
Biophysics Laboratory, International School for Advanced Studies, Via Beirut 2-4, 34014 Trieste, Italy

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Abstract

During development, in the CA1 hippocampal region, long-term potentiation (LTP) starts appearing at postnatal (P) day 7 and reaches its maximal expression towards the end of the second postnatal week. However, LTP is often preceded by long-term depression (LTD), an activity-dependent and long-lasting reduction of synaptic strength. LTD can be induced by sustained, low-frequency stimulation of the afferent pathway and is dependent on activation of *N*-methyl-D-aspartate (NMDA) receptors. We report here that, in the CA3 hippocampal region, during a critical period of postnatal development, between P6 and P14, a high-frequency stimulation train (100 Hz, 1 s) to the mossy fibres in the presence of the NMDA receptor antagonist (+)-3-(2-carboxy-piperazin-4-yl)-propyl-1-phosphonic acid (CPP; 20 μM) induced LTD. The depression of the amplitude of the field excitatory postsynaptic potential (EPSP) was 28 ± 7% (n = 21). This form of LTD was NMDA-independent and synapse-specific. When a tetanus was applied in the presence of CPP and 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; 50 μM), which blocked the field EPSP, it failed to induce LTD upon washout of CNQX. LTD was probably postsynaptic in origin since it did not affect paired-pulse facilitation. A rise in extracellular calcium concentration (from 2 to 4 mM) produced LTP instead of LTD. At the end of the second postnatal week, the same high-frequency stimulation train to the mossy fibres induced LTP as in adult neurons. Functional changes in synaptic connections during development may control membrane depolarization and the amount of intracellular calcium necessary to trigger either LTD or LTP.

Introduction

Use-dependent changes in synaptic strength such as those occurring during long-term potentiation (LTP; Bliss and Collingridge, 1993; Malenka and Nicoll, 1993) or long-term depression (LTD; Artola and Singer, 1993) are essential for information storage in the brain. In particular these processes contribute to the formation and consolidation of synaptic contacts and to the final organization of neuronal circuitry during development (Bear *et al.*, 1987). In the CA1 region of the hippocampus, low-frequency stimulation of the Schaffer collaterals, maintained over a prolonged period of time, induces an *N*-methyl-D-aspartate (NMDA)-dependent form of LTD (Dudek and Bear, 1992; Kirkwood *et al.*, 1993). This form of LTD, which is more pronounced in early postnatal life (Dudek and Bear, 1993), appears to be synapse-specific and saturable, and is prevented by loading the cell with the calcium chelator 1,2-bis(2-aminophenoxyethane-*N*,*N*,*N*′,*N*′-tetra-acetic acid (BAPTA; Mulkey and Malenka, 1992). LTD precedes the developmental onset of LTP (Dudek and Bear, 1993), which reaches its maximal expression towards the end of the second postnatal week (Harris and Teyler, 1984; Jackson *et al.*, 1993). In contrast, no information is available concerning the developmental changes in activity-dependent processes in the CA3 hippocampal region. In the adult hippocampus, in the CA3 region, two distinct forms of LTP have been characterized, depending on the pathways which are activated. A high-frequency stimulation (HFS) train to the associative–commissural pathway induces LTP which requires activation of NMDA receptors, whereas the same stimuli to the mossy fibre (MF) pathway produces LTP which is NMDA-independent (Zalutsky and Nicoll, 1990). We now report that, during a restricted period of postnatal life, between postnatal day (P) 6 and P14, a high-frequency train to the mossy fibres induces LTD instead of LTP. This form of LTD is homosynaptic, is independent of NMDA receptor activation and probably requires a rise in intracellular calcium through high voltage-activated calcium channels. After the second week of age, the same high-frequency train of stimuli induces LTP as in adult neurons.

Materials and methods

Experiments were performed on hippocampal slices obtained from P6–P24 (P0 is the day of birth) Wistar rats. The method for preparing

Correspondence to: E. Cherubini as above

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and maintaining the slices has been reported previously (Cherubini *et al.*, 1991). Briefly, rats were anaesthetized with an intraperitoneal injection of urethane and decapitated. The brain was quickly removed from the skull and the hippocampi were dissected free. Transverse 500–600 μM thick slices were cut with a tissue chopper and incubated at 33–34°C in oxygenated artificial cerebrospinal fluid (ACSF) of the following composition (in mM): NaCl, 126; KCl, 3.5; NaH_2PO_4, 1.2; $MgCl_2$, 1.3; $CaCl_2$, 2; $NaHCO_3$, 25; glucose, 11. The ACSF was equilibrated with 95% O_2 and 5% CO_2 (pH 7.3). Following a recovery period (1–3 h) one slice was transferred to a recording chamber in which it was continuously superfused at 33–34°C with oxygenated ACSF at a rate of 3 ml/min.

Extracellular field potentials were recorded with 2 M NaCl-filled microelectrodes (resistance 2–5 MΩ) positioned in the stratum radiatum. The mossy fibres were stimulated at 0.05 Hz using bipolar twisted NiCr-insulated electrodes (50 μm o.d.) which were positioned on the mossy fibre tract, close to the recording electrode. Due to the complexity of the dentate gyrus CA3 circuitry (Claiborne *et al.*, 1993) and to the small number of mossy fibres present in young animals, a site that produced a synaptic response with minimal stimulation current was searched. Recording sites close to the dentate gyrus were preferred (Regehr and Tank, 1991).

Drugs were dissolved in ACSF and applied through a three-way tap system by changing the superfusion solution to one which differed only in its content of drug(s). The ratio of flow rate to bath volume ensured complete exchange within 1 min. Drugs used were (+)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP; gift of Dr P. L. Herrling, Sandoz), 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; Tocris) and nifedipine (Sigma).

If not otherwise stated, results are presented as mean ± SD.

Results

The pyramidal cells of the CA3 hippocampal region receive two main anatomically distinct excitatory synaptic inputs: the associative–commissural and the mossy fibre pathways (Claiborne *et al.*, 1993). An HFS train to the first pathway induces LTP which requires activation of NMDA receptors, whereas the same stimulus to the MF pathway produces LTP which is NMDA-independent (Zalutsky and Nicoll, 1990). In the present work we focused our attention only on the MF-LTP; therefore all experiments were performed in the presence of the NMDA receptor antagonist CPP (20 mM) to block the associative–commissural form of LTP. At P11 a high-frequency stimulation train to the mossy fibres (100 Hz, 1 s) produced a stable and long-lasting depression of the field excitatory postsynaptic potential (EPSP). The depression attained its maximum immediately after the train, then slowly (10–15 min) declined to a stable value (37% below control level). This form of LTD was homosynaptic. In fact, when two independent fibre bundles synapsing on the same population of postsynaptic cells were alternatively stimulated, depression of synaptic strength occurred only in the synapse receiving the HFS train, whereas the control synapse was unaffected (Fig. 1). LTD was obtained in 21/32 cases (67%) in slices from P6–P14 rats. In 21 experiments, the mean reduction of the field EPSP measured 40–60 min after the HFS was 28 ± 7% (Fig. 2A). In 7/32 cases (22%), HFS of the mossy fibres induced only a short-term depression of the field EPSP. Immediately after the train, the EPSP was reduced to 31 ± 5% of the control response, then slowly returned to the control level in 25 ± 5 min. In three slices no changes in synaptic strength occurred after an HFS. There was a tendency for LTD to shift to LTP with age. As shown in Figure 2C, between P6 and P11 an HFS train

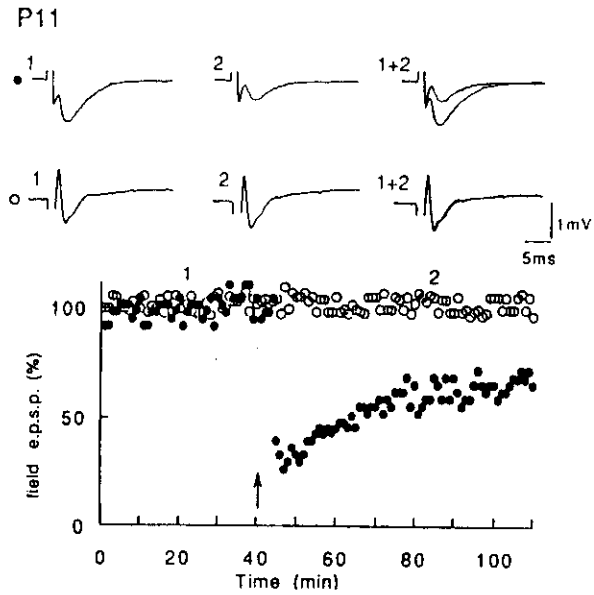

FIG. 1. HFS train to mossy fibres induces a homosynaptic NMDA-independent form of LTD. P11 rat. Two independent fibre bundles synapsing on the same population of postsynaptic cells were alternately stimulated at 0.05 Hz, but only the test pathway (filled circles) received an HFS train (arrow). The field EPSP was reduced by 37%. The control field EPSP (open circles) did not change. Insets show the average of five responses taken at the time indicated by the numbers above each graph.

to the mossy fibres induced LTD in 18 of 28 cases. Between P12 and P14 a 16 ± 11% depression was obtained in 3 of 4 cases. In the remaining slice a moderate (12%) LTP was obtained. Between P15 and P17, LTP was induced in 4 of 5 slices. It should be stressed, however, that in all cases LTP was preceded by short-term (10–15 min) depression (15 ± 5%). After P18 an LTP which was similar in all aspects to that already reported for adult neurons (Harris and Cotman, 1986; Jaffe and Johnston, 1990; Zalutsky and Nicoll, 1990) was elicited (Fig. 2B). The average increase in synaptic strength 1 h after tetanization was 69 ± 6% of control values (n = 3). The depression or potentiation of the synaptic transmission was not due to enhancement of presynaptic axon excitability since the curve relating the stimulation intensity and the amplitude of the afferent volley was unchanged after HFS. However, LTD or LTP was associated with a significant shift in the input–output curve obtained by plotting the amplitude of the afferent volley versus the amplitude or initial slope of the field EPSP (not shown). This form of LTD did not require NMDA receptor activation. It is possible, however, that activation of glutamatergic ionotropic non-NMDA receptors is important in its induction. To address this issue, in three slices (P7–P12) an HFS train was applied to the mossy fibres in the presence of CPP (20 μM) and of the non-NMDA receptor antagonist CNQX (50 μM). In these conditions, when the field EPSP was almost completely blocked the tetanus failed to induce LTD. However, the same HFS train applied after CNQX had been washed out was able to induce LTD (Fig. 3). Therefore ionotropic non-NMDA receptor activation is necessary for the induction of LTD. It is conceivable that the large amount of transmitter released upon high-frequency stimulation depolarizes the cells, leading to the entry of calcium through high voltage-activated calcium channels. To assess this hypothesis, experiments were performed in the presence of the

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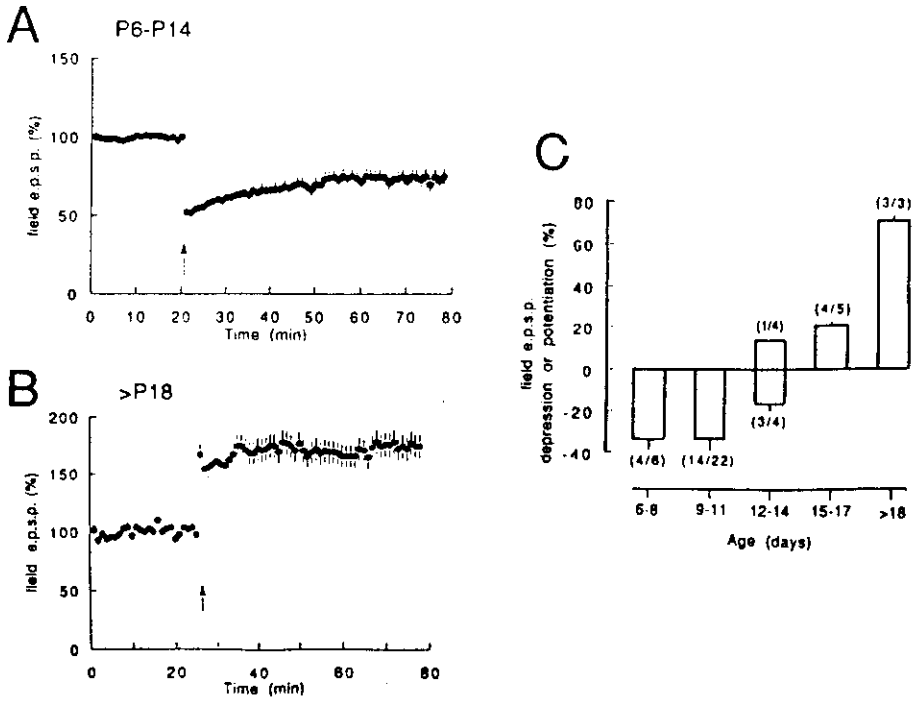

FIG. 2. LTD and LTP induced by an HFS train to the mossy fibres in young and juvenile rats. (A) At P6–P14, an HFS train produced LTD. Each point represents the mean of 21 experiments and the bar represents the SD. Synaptic strength was depressed by 28 ± 7%. (B) At P18–P24 the same protocol produced LTP. Each point represents the mean of three experiments and the bar represents the SD. Synaptic strength was potentiated by 69 ± 6%. (C) Each column in the graph represents the mean depression or potentiation of the amplitude of the field EPSP measured 40–60 min after the HFS train in different age groups. Bars represent the SD. On the top of each column is the number of slices depressed or potentiated/number of slices tested.

selective dihydropyridine-sensitive calcium channel antagonist nifedipine. Nifedipine (10 μM, 10 min) did not modify the field EPSP and failed to block LTD (n = 3). These data rule out the possibility that nifedipine-sensitive calcium channels are involved in the induction of LTD.

It has been suggested that a rise in postsynaptic calcium through NMDA receptors is necessary for LTD induction in the CA1 region of the hippocampus. However, the rise in calcium would be significantly less than that required for LTP induction (Dudek and Bear, 1992). To test whether this hypothesis could be applied also to our experiments, we examined the effects of increasing or decreasing the driving force for calcium by lowering or raising the extracellular calcium concentration $[Ca^{2+}]_o$. As shown in Figure 4, no significant changes in the amplitude or slope of the field EPSP were observed when the external calcium was raised from 2 to 4 mM. However, when an HFS train was delivered to the mossy fibres in 4 mM $[Ca^{2+}]_o$ a slight increase in synaptic strength developed over 20–30 min, reaching a steady value in ~40 min (34%). An HFS train applied again to the mossy fibres when the field EPSP amplitude had reached a steady value (in 2 mM $[Ca^{2+}]_o$) depotentiated the synaptic responses, revealing an LTD (Fig. 4). This phenomenon was observed in three slices. In some cases only a slight increase (17%, n = 2) or no change (n = 3) in synaptic efficacy was observed. It should be stressed, however, that in 4 mM $[Ca^{2+}]_o$ LTD was never obtained. On the contrary, in a low-calcium solution (0.5 mM), tetanic stimulation of the mossy fibres always (n = 3) induced LTD.

There is general agreement that LTD in several brain structures is a postsynaptic phenomenon. To test whether the expression of an

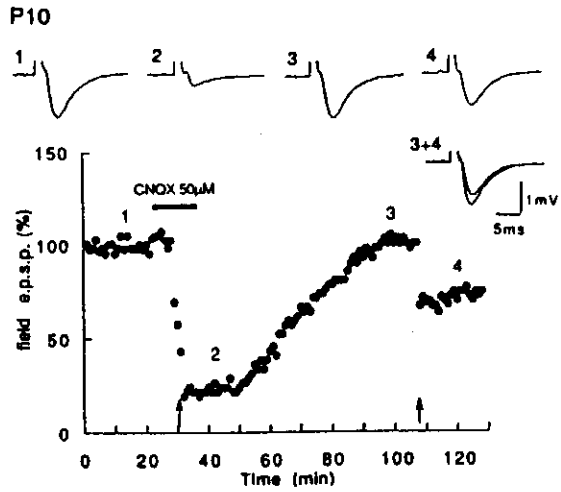

FIG. 3. LTD in young animals requires activation of glutamatergic ionotropic non-NMDA receptors. P10 animal. In the presence of CNQX (50 mM, bar) the amplitude of the field EPSP was almost completely blocked. An HFS train (arrow) delivered to the mossy fibres failed to induce LTD. Upon washout of CNQX, an HFS train induced a persistent depression of the amplitude of the field EPSP of 29%. Insets show the average of five responses taken at the times indicated by the numbers above the graphs.

MF-LTD also involves a postsynaptic site of action, experiments were performed measuring paired-pulse facilitation, which is clearly due to a presynaptic effect (Zucker, 1989). The results of one of three

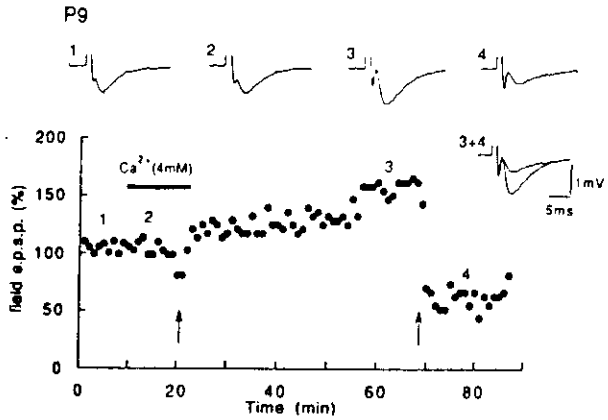

FIG. 4. Changes in synaptic efficacy in the presence of a high extracellular calcium concentration. P9 rat. In 4 mM $[Ca^{2+}]_o$ an HFS train to the mossy fibres induced potentiation of the field EPSP (34%) which reached a steady value after 40 min. At this point an HFS train delivered in 2 mM $[Ca^{2+}]_o$ markedly depotentiated the field EPSP (by 58%). Insets show the average of five responses taken at the times indicated by the numbers above the graphs.

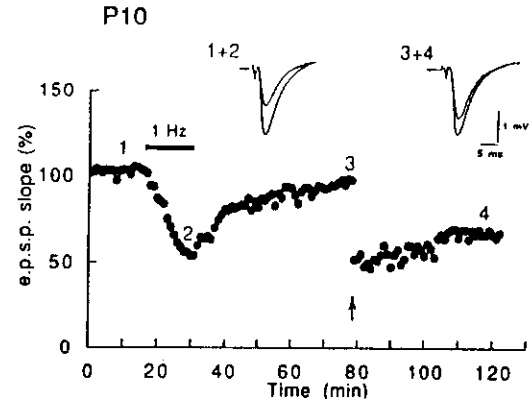

FIG. 6. Short- and long-term depression induced by different stimulation procedures. P10 rat. Low-frequency stimulation (1 Hz, 900 s) of the mossy fibres induced short-term depression; after 45 min the slope of the field EPSP returned to the prestimulus level. On the contrary, subsequent high-frequency stimulation induced long-term depression (36% below control level after 40 min). Insets show superimposed traces taken at the times indicated by the numbers above the graphs. Each trace is the average of five responses.

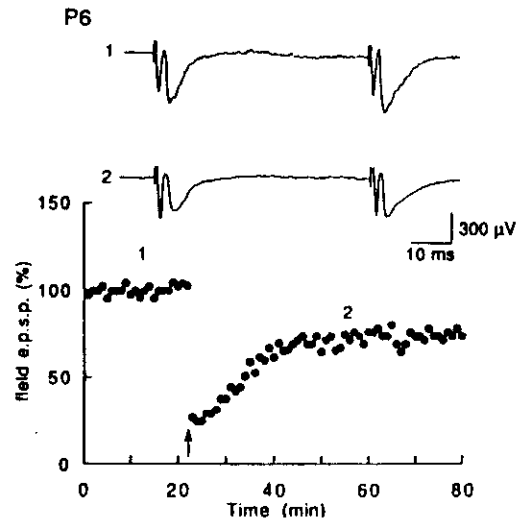

FIG. 5. Paired-pulse facilitation is not affected by LTD. P6 rat. Paired-pulse facilitation was monitored continuously before and after the induction of LTD by an HFS train. Insets are averages of five paired responses (50 ms interval) of field EPSPs evoked at the time indicated by the numbers.

experiments are shown in Figure 5. As shown in the figure, in these experiments the magnitude of paired-pulse facilitation during LTD was not affected, implying that LTD expression occurs at a site different from that involved in paired-pulse facilitation.

In the CA1 hippocampal region, LTD could be induced by a prolonged period of low-frequency stimulation (1 Hz, 900 s; Mulkey and Malenka, 1992; Dudek and Bear, 1993). We used the same protocol in order to see if we could obtain LTD (in six slices). Stimulation of the mossy fibres at 1 Hz for 900 s in the presence of CPP (20 μM) induced a depression of the amplitude of the field EPSP. The depression reached a maximum at the end of stimulation (46 ± 3%). In two slices the depression was still present after 40 min (38 and 36% respectively). In the remaining four slices, after 35 ± 5 min the amplitude of the field EPSP slowly returned to the baseline level but subsequent HFS was able to produce long-term depression (36 ± 4% after 45 min; Fig. 6). This suggests that the depression of synaptic transmission by an HFS train or by sustained low-frequency stimulation may be due to different mechanisms.

Discussion

Our results clearly show that during a critical period of postnatal development, CA3 hippocampal neurons respond to tetanic stimulation of the mossy fibres with LTD instead of LTP. This form of LTD is NMDA-independent and is therefore different from that observed in the CA1 region following sustained low-frequency stimulation of the afferent pathway (Dudek and Bear, 1992; Mulkey and Malenka, 1992). A non-NMDA type of LTD has recently been described in the CA1 hippocampal region in slices obtained from 15-day-old rats and in conditions in which LTP was blocked by NMDA receptor antagonists (Velisek *et al.*, 1993). In that case, however, the unmasked LTD was obtained with a different stimulation protocol. The stimulation protocol used in the present experiments resembled that used to induce LTD in the neocortex (Hirsch and Crepel, 1990), in the striatum (Calabresi *et al.*, 1992) or in the nucleus accumbens (Pennartz *et al.*, 1993). When the same experimental paradigm as that of Dudek and Bear (1992) was used, LTD was less effective and short-term depression was often obtained. In analogy to short-term potentiation (Malenka, 1991), the mechanisms underlying this transient form of depression may be different from those involved in LTD .

It is possible that, like other forms of LTD (Hirsch and Crepel, 1991; Wickens and Abraham, 1991), a rise in calcium through voltage-dependent calcium channels is responsible for the induction of MF-LTD. Although the data with nifedipine were not conclusive, we cannot exclude the possibility that other voltage-dependent calcium channels play a crucial role in the induction of LTD. A rise in intracellular calcium, released either from intracellular stores following activation of metabotropic receptors (Nakanishi, 1992) or through the mechanism of calcium-induced calcium release (Berridge, 1993), may also be involved. Evidence in favour of metabotropic receptor activation in LTD induction has been presented (Stanton *et al.*, 1991;

Kato, 1993). In keeping with this, it has been recently shown that (+)-α-methyl-4-carboxyphenylglycine, a specific antagonist of the metabotropic glutamate receptor, can prevent the elicitation of LTD in the CA1 region by low-frequency stimulation, following prior saturation of LTP (Bashir *et al.*, 1993). Our experiments do not allow us to specify if calcium changes occur at the pre- or postsynaptic level. Intracellular experiments using calcium chelating agents may be useful to elucidate this problem. However, as already shown for LTP, the complex circuitry of the CA3 region would make it difficult to interpret the data. In fact, even if the induction of MF-LTP or LTD were to involve a postsynaptic mechanism, this would be undetectable if the synapse under observation were not the site of the plasticity (Claiborne *et al.*, 1993). Like other forms of LTD (Brocher *et al.*, 1992; Hirsch and Crepel, 1992; Mulkey and Malenka, 1992; Xie *et al.*, 1992), it is possible that the MF-LTD observed in immature neurons is dependent on postsynaptic calcium. In favour of a postsynaptic site of action are the experiments with paired-pulse facilitation, which have shown the lack of effect of LTD on this phenomenon, suggesting that the expression of LTD takes place at a site different from that of paired-pulse facilitation. We can argue whether LTD and LTP represent the same variable, since LTD, triggered in ACSF containing a normal calcium concentration, can be reversed to LTP in a high-calcium solution. In keeping with a previous report (Mulkey and Malenka, 1992), the direction of synaptic change would be determined by the extracellular calcium concentration. This in turn would influence the magnitude of calcium entry through voltage-dependent calcium channels, the time course of calcium signals and the calcium-buffering capacity of the cell. Changes in calcium-buffering capacity of CA3 pyramidal neurons during development (Cherubini *et al.*, 1991) may account for the present results. Moreover, the MF-LTD closely resembles that described in the visual cortex, where the same tetanic stimulation can induce either LTP or LTD depending on the level of depolarization of the postsynaptic neurons (Artola *et al.*, 1990). Functional changes in synaptic connections may limit depolarization and calcium fluxes during development. In the CA3 region dendritic spines start appearing at P4–P5 and reach adult levels at P20 concomitant with the maturation of the mossy fibres (Gaiarsa *et al.*, 1992). These latter may have an inductive role in spine formation. Synaptic activity in turn would regulate protein phosphorylation and intracellular calcium (Mulkey *et al.*, 1993), and this may be the critical point leading to the development of LTD or LTP in early and late postnatal life respectively.

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Abbreviations

ACSF	artificial cerebrospinal fluid
CA1	cornu ammonis 1
CA3	cornu ammonis 3
CNQX	6-cyano-7-nitroquinoxaline-2,3-dione
CPP	(+)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid
EPSP	excitatory postsynaptic potential
HFS	high-frequency stimulation
LTD	long-term depression
LTP	long-term potentiation
MF	mossy fibre
NMDA	*N*-methyl-D-aspartate

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