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Long-lasting modulation of the induction of LTD and LTP in rat hippocampal CA1 by behavioural stress and environmental enrichment

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Abstract

Behavioural experience (e.g. chronic stress, environmental enrichment) can have long-lasting effects on cognitive functions. Because activity-dependent persistent changes in synaptic strength are believed to mediate memory processes in brain areas such as hippocampus, we tested whether behaviour has also long-lasting effects on synaptic plasticity by examining the induction of long-term potentiation (LTP) and long-term depression (LTD) in slices of hippocampal CA1 obtained from rats either 7–9 months after social defeat (behavioural stress) or 3–5 weeks after 5-week exposure to environmental enrichment. Compared with age-matched controls, defeated rats showed markedly reduced LTP. LTP was even completely impaired but LTD was enhanced in defeated and, subsequently, individually housed (during the 7–9-month period after defeat) rats. However, increasing stimulus intensity during 100-Hz stimulation resulted in significant LTP. This suggests that the threshold for LTP induction is still raised and that for LTD lowered several months after a short stressful experience. Both LTD and LTP were enhanced in environmentally enriched rats, 3–5 weeks after enrichment, as compared with age-matched controls. Because enrichment reduced paired-pulse facilitation, an increase in presynaptic release, facilitating both LTD and LTP induction, might contribute to enhanced synaptic changes. Consistently, enrichment reduced the number of 100-Hz stimuli required for inducing LTP. But enrichment may also actually enhance the range of synaptic modification. Repeated LTP and LTD induction produced larger synaptic changes in enriched than in control rats. These data reveal that exposure to very different behavioural experiences can produce long-lasting effects on the susceptibility to synaptic plasticity, involving pre- and postsynaptic processes.

Introduction

Behavioural experience modulates learning and memory. Exposure to acute as well as prolonged stress produces cognitive deficits (reviewed in de Kloet *et al*., 1999; McEwen, 1999; Kim & Diamond, 2002) that can be long-lasting (Bodnoff *et al*., 1995; Von Frijtag *et al*., 2000; Reijmers *et al*., 2001). Conversely, environmental enrichment, a paradigm to examine the effects of environmental 'experience' – a combination of complex inanimate and social interactions (Rosenzweig *et al*., 1978; Rosenzweig & Bennett, 1996) – on the brain, enhances memory function (reviewed in Van Praag *et al*., 2000).

Learning is thought to occur through long-lasting, activity-dependent changes in synaptic efficacy. Two opposite synaptic modifications, long-term potentiation (LTP) and long-term depression (LTD), have been identified so far. In many brain areas, including the hippocampus and neocortex, the direction and the degree of synaptic changes depend primarily on postsynaptic depolarization: LTD is obtained following low levels of depolarization whereas LTP is induced by stronger ones (Dunwiddie & Lynch, 1978; Artola *et al*., 1990; Dudek & Bear, 1992). But the susceptibility to synaptic plasticity also depends on behaviour. Acute (Foy *et al*., 1987; Shors *et al*., 1989; Xu *et al*., 1997; but see Meshes *et al*., 1999) and chronic stressors (Gerges *et al*., 2001, 2004; Pavlides *et al*., 2002; Alfarez *et al*., 2003) virtually abolish the induction of LTP in hippocampus. Concomitantly, LTD is facilitated (Kim *et al*., 1996; Xu *et al*., 1997). Cognitively stimulating environment enhances LTP in CA1 (Duffy *et al*., 2001), but decreases that in dentate gyrus (Foster *et al*., 1996, 2000). Regular physical activity, in consequence of environmental enrichment, has no effect on synaptic transmission in CA1 but enhances LTP in dentate gyrus (Van Praag *et al*., 1999).

While it is clear that behavioural experience modulates synaptic plasticity, it is not known whether such modulation can be long-lasting. Synaptic plasticity is usually assessed during or soon after modified behavioural experiences, and behavioural paradigms in which this issue has been addressed appear to have only short-lasting

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effects on synaptic plasticity: behavioural stress impairs LTP for 1–2 days (Garcia *et al.*, 1997; Shors *et al.*, 1997) and facilitates LTD for 20–95 min (Xu *et al.*, 1997). Therefore, we presently examined whether the susceptibility to synaptic plasticity in the CA1 area of hippocampus is still modified: (i) 7–9 months after social defeat (associated with various post-stress housing conditions); and (ii) 3–5 weeks after environmental enrichment. Social defeat consists of introducing a male rat (the 'intruder') into the territory of a residential aggressive conspecific (the 'resident'). The uncontrollable and unpredictable occurrence of attacks by the resident and the inability to inhibit fights results in a severe stress for the intruder (Fokkema & Koolhaas, 1985; Sgoifo *et al.*, 1994; Tornatzky & Miczek, 1994; Haller *et al.*, 1995; Meehan *et al.*, 1995; Van den Berg *et al.*, 1999). In the second behavioural paradigm, rats exposed to environmental enrichment (cages containing stimulus objects) for 5 weeks were subsequently housed in standard laboratory conditions for another 3–5 weeks. Animals exposed to each behavioural paradigm were compared with corresponding age-matched controls.

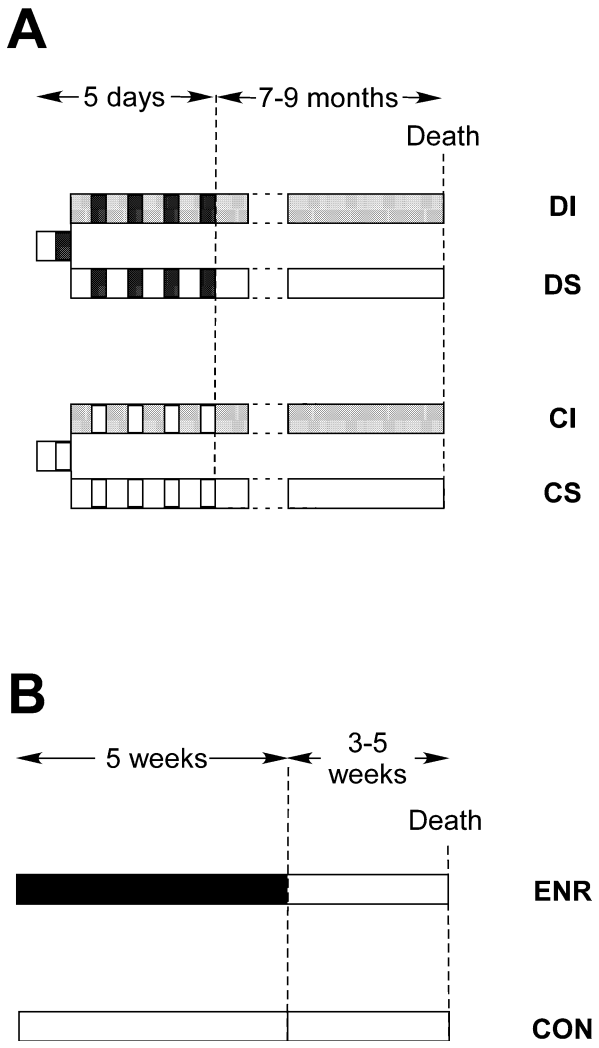

FIG. 1. Schematic representation of the experimental design in social stress/post-stress housing condition (A) and environmental enrichment experiments (B). (A) Adult rats were subjected to either resident–intruder sessions (black rectangles) or control treatments (white rectangles) on 5 consecutive days. Immediately after the first session, rats were housed either individually (grey bar) or socially (2 rats per cage; empty bar). This procedure resulted in four experimental groups: socially defeated rats that were either individually (DI) or socially (DS) housed; and control rats that were either individually (CI) or socially (CS) housed. After 7–9 months, rats were decapitated. (B) Seven-week-old rats were housed under either environmentally enriched (black bar) or control conditions (standard cages; empty bar) in groups of 5 rats for a period of 5 weeks. After housing under enriched or control conditions, all rats were transferred into standard cages (5 rats per cage in unchanged configuration) for 3–5 weeks. This resulted in two experimental groups: environmentally enriched (ENR) and control (CON) rats. (A, B) During the dark phase of the light cycle rats were decapitated in a separate test room, and hippocampal slices were prepared for electrophysiological recordings.

Materials and methods

Housing condition

Male Wistar rats (GDL, Utrecht, The Netherlands) were housed under a reversed day : night cycle (lights on at 19.00 h and off at 07.00 h) in a temperature-controlled room (21 ± 1 °C). Food and water were available *ad libitum*. At the beginning of the social stress and environmental enrichment experiments, rats were housed in, respectively, Macrolon type III (42.5 × 26.5 × 18.5 cm; l × w × h) or IV (59.5 × 38 × 20 cm; l × w × h) cages. Cages were cleaned weekly unless indicated otherwise. The experimental procedures were approved by the Ethical Committee for Animal Experiments of Utrecht University.

Social stress experiment

Adult rats (300–350 g) were submitted to either social defeat or control treatment (Fig. 1A). The social defeat procedure consisted of daily resident–intruder sessions on five consecutive days. During each session (20 min), the experimental rat (the 'intruder') was placed into the territory (63 × 25 × 33 cm; l × w × h) of a dominant (the 'resident') male Tyron Maze-Dull rat (TMD-S3; CDL, Maastricht, The Netherlands). Each session consisted of a pre-fight (5 min), fight (5 min) and post-fight phase (10 min), as previously described (Von Frijtag *et al.*, 2000). During pre- and post-fight phases, the intruder was separated from the resident by a transparent, perforated plastic partition-wall. The fight phase was initiated and terminated by either removing or replacing the partition-wall. In all cases the experimental rat was attacked and lost the fight. Control rats were placed in similar cages for 20 min. Immediately after the first session, rats were housed in Macrolon type III cages either individually or socially (2 rats per cage). This procedure resulted in four experimental groups: socially defeated rats that were either individually (DI) or socially (DS) housed; and control rats that were either individually (CI) or socially (CS) housed (Fig. 1A). After 7–9 months of such housing conditions, rats were decapitated during the dark phase of the light cycle in a separate test room, and hippocampal slices were prepared for electrophysiology.

Environmental enrichment experiment

Seven-week-old rats were housed under either environmentally enriched or control conditions in groups of 5 rats for a period of 5 weeks (Fig. 1B). The environmentally enriched cages were developed in our laboratory (Van der Harst *et al.*, 2003a,b). They consisted of Macrolon type IV cages that were heightened with a metal rim of 8 cm. Several objects that increased the surface of the cage by 45% were placed into the cages: compartmentalization was achieved by a mesh-wire shelter (10 × 11 × 24.2 cm; h × w × l) and a tunnel-shaped metal object (14.5 × 16 × 32 cm; h × w × l). The latter object had several passages at the sides and on top, and some small holes through which pieces of gnawing-wood were inserted. A metal bin

(5 × 12 × 32 cm; h × w × l) was located under the food-hopper and was filled with old bedding from the cage when the remainder of the cage was cleaned. Control rats were housed in unmodified Macrolon type IV cages (5 rats per cage). After housing under control or enriched conditions, all rats were transferred into standard Macrolon type IV cages (5 rats per cage in unchanged configuration) for 3–5 weeks. This resulted in two experimental groups: environmentally enriched (ENR) and control (CON) rats (Fig. 1B). After 3–5 weeks, rats were decapitated during the dark phase of the light cycle in a separate test room, and hippocampal slices were prepared for electrophysiological recordings.

Electrophysiological recordings

After a short period of gas anaesthesia (isoflurane), rats were decapitated. The brains were rapidly removed and immersed into chilled medium. Hippocampal slices (450 μm thick) were prepared as previously described (Kamal *et al*., 1998). The slices were allowed to recover for at least 1 h at room temperature in artificial cerebrospinal fluid (ACSF) containing (in mM): NaCl, 124; KCl, 3.3; KH_2PO_4, 1.2; $MgSO_4$, 1.3; $CaCl_2$, 2.5; $NaHCO_3$, 20; glucose, 10.0; saturated with 95% O_2/5% CO_2. One slice was then transferred into the recording chamber (submerged type) where it was perfused with ACSF (2 mL/min) and maintained at 30 °C.

The Schaffer collateral-commissural pathway was stimulated using a bipolar stainless steel electrode (tip interval: 100 μm) placed in the stratum radiatum of the CA1 region, and field excitatory postsynaptic potentials (fEPSPs) were recorded using a low-resistance glass microelectrode (tip diameter: 3–5 μm; 0.5 MΩ, filled with ACSF) also placed in the stratum radiatum. Before each experiment, we determined stimulus intensities that elicited threshold and maximum fEPSP by gradually increasing stimulus intensity until the fEPSP amplitude reached a saturated level. Only those slices that displayed maximal fEPSP larger than 1 mV were included in the study. The stimulus intensity was then adjusted to give fEPSP amplitudes of about 50% of maximum fEPSPs and responses were elicited at 0.03 Hz (test stimulation).

In all experiments, baseline synaptic transmission was monitored for 15 min before delivering high- or low-frequency stimulations (HFS and LFS). HFS consisted of a 1-s-long train of 100-Hz stimulation at test intensity. LFS consisted of a 15-min-long train of 1-Hz stimulation at test intensity. To determine the frequency–response curve for the induction of synaptic plasticity in CS and DI rats, 900 pulses were delivered at 0.05, 1, 5, 10, 50 and 100 Hz. High-intensity HFS consisted of four 1-s-long trains of 100-Hz stimulation (intertrain interval = 10 s), the stimulus intensity during HFS being 1.5 × test intensity. Pulse–response curves for the induction of LTP in CON and ENR rats were determined by applying a varying number (ranging from 5 to 100) of 100-Hz stimulations. Repeated LFS in CON and ENR rats consisted of two 15-min-long trains of 1-Hz stimulation (intertrain interval = 15 min) at test intensity. Responses to test stimulation were monitored for 30–60 min after HFS or LFS as indicated in the text. To determine the dynamic range of synaptic plasticity in CON and ENR rats, three HFSs (1-s-long trains of 100-Hz stimulation) were repeated at 20-min intervals, followed by four LFSs (5-min-long trains of 1-Hz stimulation) at 20-min intervals.

In control and environmentally enriched rats, responses to paired-pulse stimulation (20, 50 and 100 ms intervals) were also recorded. The paired-pulse ratio was expressed as the percentage increase of the second response relative to the first one.

Statistical analysis

Field EPSP slopes (test frequency: 0.03 Hz) were averaged over 5-min intervals and expressed as percentages of the mean fEPSP slope measured during the 15-min baseline period prior to the induction protocol. Grouped data are expressed as means ± SEM unless otherwise stated. For statistical analysis, the non-parametric Wilcoxon's signed ranks test, two-way ANOVA followed by Duncan's tests when appropriate, one-way ANOVA and one-way ANOVA with repeated-measures followed by a one-way ANOVA when appropriate were used as indicated.

Results

Because induction of both LTD and LTP is age-dependent (see Dudek & Bear, 1993; Norris *et al*., 1996; Shankar *et al*., 1998; for review see Foster, 1999, 2002), we compared rats subjected to either social defeat associated with various housing conditions or environmental enrichment with age-matched control animals (see Materials and methods, and Fig. 1). Electrophysiological experiments on behaviourally modified rats were interleaved with those on control ones.

Social defeat and post-stress housing condition

We initially tested the effect of HFS (1-s-long train of 100-Hz stimulation) on synaptic transmission in CA1 slices obtained from socially defeated and individually housed (DI; $n = 6$), socially defeated and socially housed (DS; $n = 5$), control and individually housed (CI; $n = 5$), and control and socially housed rats (CS; $n = 6$) (Fig. 2A). HFS produced a significant potentiation in CS (199.4 ± 7.4% of baseline; 60 min after HFS; Wilcoxon's signed ranks test: $z = -2.2$, $P = 0.028$), CI (136.7 ± 7.6% of baseline; $z = -2.0$, $P = 0.043$) and DS (125.2 ± 4.1% of baseline; $z = -2.0$, $P = 0.043$) rats. On the other hand, it failed to produce any potentiation in DI rats (96.4 ± 2.8% of baseline). Two-way ANOVA revealed a significant interaction of social defeat and housing conditions (defeat × housing condition: $F_{1,18} = 8.3$, $P = 0.010$). *Post-hoc* comparisons (Duncan's test) showed that fEPSP slopes in DI rats were significantly ($P < 0.05$) smaller than those in all other groups. DS and CI groups exhibited similar degrees of potentiation that were nevertheless significantly ($P < 0.05$) smaller than that in CS rats.

We also tested the effect of LFS (15-min-long train of 1-Hz stimulation) on synaptic transmission in CA1 slices obtained from the same four groups (Fig. 2B). LFS produced a significant LTD only in DI rats (82.3 ± 5.1% of baseline; 60 min after LFS; Wilcoxon's signed ranks test: $z = -2.2$, $P = 0.028$). In neither DS (102.8 ± 5.2% of baseline), CI (105.3 ± 1.9% of baseline) nor CS rats (95.8 ± 2.6% of baseline) was synaptic transmission affected. Two-way ANOVA revealed a significant interaction of social defeat and housing conditions (defeat × housing condition: $F_{1,16} = 10.7$, $P = 0.005$). *Post-hoc* comparisons (Duncan's test) showed that fEPSP slopes in DI rats were significantly smaller ($P < 0.05$) than those in all other groups.

The action of social defeat and/or individual housing on the induction of synaptic plasticity is not a secondary effect of changes in baseline synaptic transmission. Stimulus intensity was selected for baseline measurements that yielded about half of the maximal response (see Material and methods). There was no difference in the amplitude and slope of fEPSPs recorded in the four groups before induction protocols. The slopes of baseline fEPSPs were 0.44 ± 0.09, 0.46 ± 0.04, 0.47 ± 0.11 and 0.47 ± 0.09 mV/ms (mean ± SD) in DI, DS, CI and CS rats, respectively.

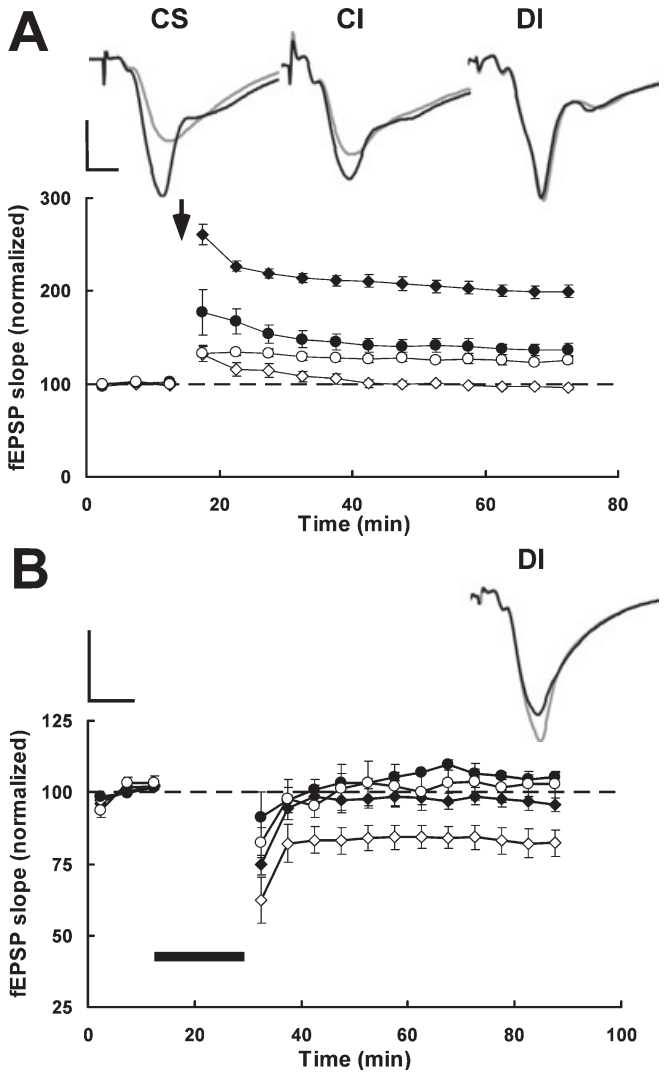

FIG. 2. Occurrence of LTP and LTD is critically dependent on social defeat and housing conditions. (A) Graph displaying the mean (± SEM) of field excitatory postsynaptic potential (fEPSP) slope over time for the four groups of rats: socially defeated and individually housed rats (DI: empty diamonds; $n = 6$), socially defeated and socially housed rats (DS: empty circles; $n = 5$), control and individually housed rats (CI: filled circles; $n = 5$), and control and socially housed rats (CS: filled diamonds; $n = 6$). fEPSP slopes (test frequency: 0.03 Hz) are averaged over 5-min intervals. HFS (1-s-long train of 100-Hz stimulation at test intensity) was applied at the vertical arrow. The effect of behavioural experience on synaptic plasticity was most pronounced in DI rats that showed no significant LTP. *Inset*: Superimposed averages of 15 consecutive fEPSPs (0.03 Hz) recorded before (grey) and 60 min after (black) HFS from representative CS (left), CI (middle) and DI (right) rats. (B) Graph displaying the mean (± SEM) of fEPSP slope over time in the four groups of rats: DI, DS, CI and CS. Symbols are as in (A). LFS (15-min-long train of 1-Hz stimulation) was applied at the horizontal bar. LFS induced LTD only in DI rats. *Inset*: Superimposed averages of 15 consecutive fEPSPs (0.03 Hz) recorded before (grey) and 60 min after (black) LFS from a representative DI (right) rat. Scale bars: 5 ms, 1 mV (A and B).

Thus, the effect of both 1-Hz and 100-Hz stimulations on hippocampal synaptic transmission appears to critically depend on the behavioural experience of rats. The function relating synaptic plasticity to stimulation frequency is actually continuous (Dunwiddie & Lynch, 1978; Dudek & Bear, 1992; Mayford *et al.*, 1995). How is this frequency–response function for synaptic plasticity affected by social defeat and individual housing? We addressed this issue in a new series of experiments by comparing the frequency–response functions of DI ($n = 6$) and CS rats ($n = 6$) (Fig. 3). In CS rats, low frequencies (1 and 5 Hz) had no effect on fEPSPs (1 Hz: 97.3 ± 7.0%; and 5 Hz: 100.2 ± 3.1% of baseline, 30 min after LFS), whereas higher frequencies induced LTP (50 Hz: 152.1 ± 7.4%; and 100 Hz: 259.0 ± 27.6% of baseline; Wilcoxon's signed ranks test for 50 and 100 Hz: $z = -2.2$, $P = 0.028$). In DI rats, conversely, low frequencies induced a robust LTD (1 Hz: 68.4 ± 6.9%; and 5 Hz: 79.7 ± 4.8% of baseline; for 1 and 5 Hz: $z = -2.2$, $P = 0.028$). But high frequencies failed to induce LTP (50 Hz: 101.6 ± 2.8%; and 100 Hz: 104.9 ± 3.1% of baseline). One-way ANOVA revealed a significant difference between DI and CS rats at both low (1 Hz: $F_{1,10} = 8.6$, $P = 0.015$; 5 Hz: $F_{1,10} = 12.8$, $P = 0.005$) and high frequencies (50 Hz: $F_{1,10} = 41.0$, $P = 0.000$; 100 Hz: $F_{1,10} = 30.8$, $P = 0.000$). These results thus confirm our findings in the first series of experiments: in DI rats, HFSs fail to produce LTP whereas LFSs are able to induce LTD. Similar impairment in LTP and facilitation of LTD have been observed following other types of behavioural stress (Foy *et al.*, 1987; Shors *et al.*, 1989; Kim *et al.*, 1996; Xu *et al.*, 1997).

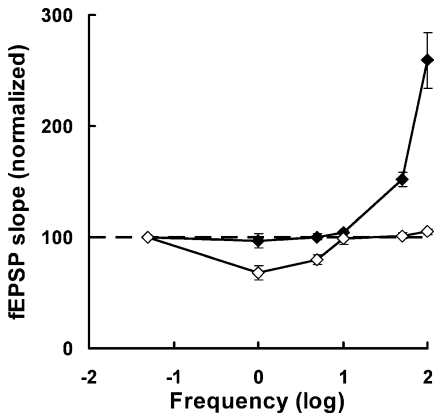

FIG. 3. Frequency–response functions for the induction of synaptic plasticity in hippocampal CA1 in CS (filled diamonds; $n = 6$) and DI rats (empty diamonds; $n = 6$).

The two previous series of experiments show that HFS fails to induce LTP in DI rats. One possibility is that molecular mechanisms that are required for synaptic potentiation are impaired by social defeat and subsequent individual housing. Another hypothesis is that LTP or a LTP-like process occurs in the hippocampus during behavioural stress. If synaptic transmission varies within a fixed range and stress elevates basal synaptic transmission to the ceiling of this range, then subsequent attempts at electrically induced LTP after stress should not produce LTP (see Kim *et al.*, 1996; Rioult-Pedotti *et al.*, 2000). Yet another possibility is that the threshold for inducing LTP is higher in stressed than in control animals. To test for this possibility, we increased stimulus intensity during HFS (Fig. 4A). High-intensity HFS (four 1-s-long trains of 100-Hz stimulation, intertrain interval = 10 s, at 1.5 × test intensity) caused a significant LTP in DI rats (150.7 ± 12.9% of baseline, 60 min after HFS; Wilcoxon's signed ranks test: $z = -2.2$, $P = 0.028$; $n = 6$). However, the degree of LTP in DI rats was still smaller than that in CS rats (218.4 ± 40.0% of baseline, $z = -2.2$, $P = 0.028$; $n = 6$), though the difference between the two groups was not significant (one-way ANOVA: $F_{1,10} = 2.6$, $P = 0.136$). Thus, HFS, that had no effect on synaptic transmission at test intensity, produced a significant LTP when stimulus intensity was increased (Fig. 4B). This result is consistent with the hypothesis that behavioural stress elevates the threshold for inducing LTP.

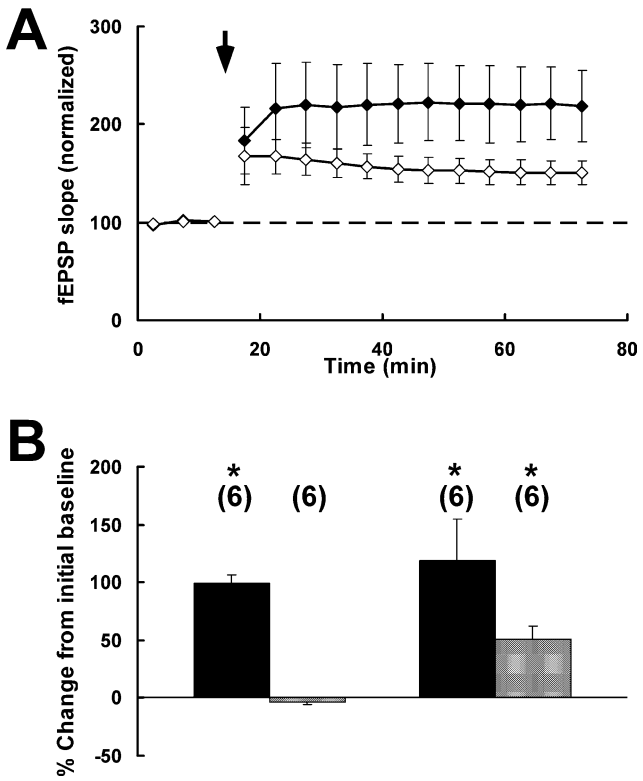

FIG. 4. High-intensity HFS can induce LTP in DI rats. (A) Graph displaying the mean (± SEM) of field excitatory postsynaptic potential (fEPSP) slope over time in CS (filled diamonds; $n = 6$) and DI (empty diamonds; $n = 6$) rats. Four high-intensity (1.5 × test intensity) HFSs (1-s-long trains of 100-Hz stimulation, intertrain interval = 10 s) were applied at the vertical arrow. (B) Bar chart summarizing the changes in mean fEPSP slope (+ SEM), of CS (black bars) and DI (grey bars) rats measured 60 min after test (left) and high-intensity HFS (right), and expressed as percentage of baseline amplitude. The number of rats is indicated above each bar. *The change is significant ($P < 0.05$).

Environmental enrichment

We first tested the effect of HFS (1-s-long train of 100-Hz stimulation) on synaptic transmission in hippocampal slices obtained from socially enriched (ENR; $n = 6$) and control rats (CON; $n = 6$) (Fig. 5A). HFS induced LTP in both ENR (169.1 ± 3.8% of baseline, 30 min after HFS) and CON rats (152.3 ± 5.4% of baseline) (Wilcoxon's signed ranks test for ENR and CON: $z = -2.2$, $P = 0.028$), but the degree of potentiation was significantly larger in ENR than in CON rats (one-way ANOVA: $F_{1,10} = 5.4$, $P = 0.043$).

We also tested the effect of LFS on synaptic transmission in ENR ($n = 5$) and CON rats ($n = 8$). Mockett *et al*. (2002) have shown that the degree of LTD increases non-linearly with the number of pulses in the LFS. Therefore, to obtain larger synaptic changes in this series of experiments, LFS (15-min-long train of 1-Hz stimulation) was repeated twice at 15-min interval. LFSs resulted in LTD in both ENR (62.8 ± 4.0% of baseline, 60 min after the last LFS, Wilcoxon's signed ranks test $z = -2.0$, $P = 0.043$) and CON rats (84.8 ± 4.2% of baseline, $z = -2.2$, $P = 0.025$) (Fig. 5C). But, again, the degree of the synaptic modification − here depression − was larger in ENR than in CON rats (one-way ANOVA: $F_{1,11} = 12.7$, $P = 0.004$).

There was no difference in the amplitude and slope of fEPSPs recorded in ENR and CON rats before induction protocols. The slopes of baseline fEPSPs were 0.37 ± 0.06 and 0.39 ± 0.07 mV/ms (mean ± SD) in ENR and CON rats, respectively.

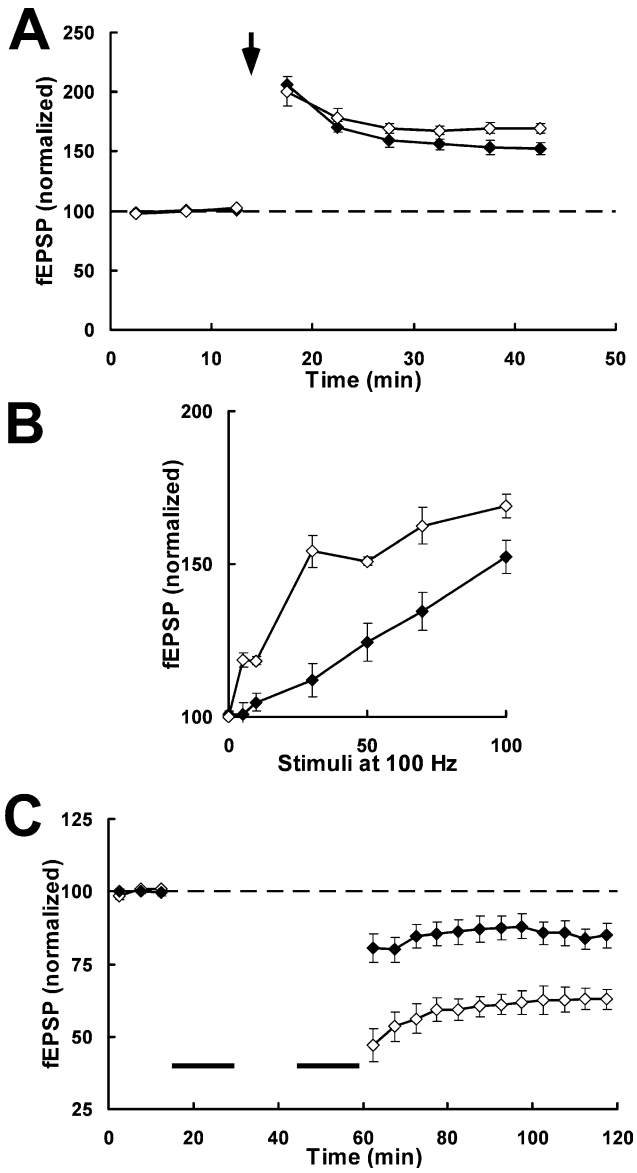

FIG. 5. Environmental enrichment enhances both LTP and LTD. (A) Graph displaying the mean (± SEM) of field excitatory postsynaptic potential (fEPSP) slope over time for the two groups of rats: environmentally enriched (ENR: empty symbols; $n = 6$) and control (CON: filled symbols; $n = 6$) rats. HFS (1-s-long train of 100-Hz stimulation at test intensity) was applied at the vertical arrow. (B) Function relating the synaptic change to the number of stimuli during HFS in ENR ($n = 6$) and CON rats ($n = 6$). Symbols are as in (A). ENR rats showed a lower threshold for LTP induction than CON ones. (C) Graph displaying the mean (± SEM) of fEPSP slope over time for the two groups of rats: ENR ($n = 5$) and CON ($n = 8$). Symbols are as in (A). Two LFS (15-min-long train of 1-Hz stimulation, intertrain interval = 15 min) were applied at horizontal bars. Repeated LFSs result in larger LTD in ENR than in CON rats.

Both LTP and LTD were larger in ENR compared with CON rats. A possible explanation is a facilitation of the induction of both LTD and LTP in ENR rats. To detect a variation in the threshold for the induction of LTP, one can assess changes in the frequency–response function for synaptic plasticity. Increase and decrease in the threshold for LTP shifts the LTD–LTP crossover point to the right and to the left, respectively (see examples in Mayford *et al*., 1995; Kirkwood *et al*., 1996; Wang & Wagner, 1999). However, here, such a shift might be obscured as, in addition, the frequency–response function for synaptic

plasticity of ENR rats crosses that of CON rats between 1 and 100 Hz, owing to the larger LTP and LTD in ENR compared with CON rats. Therefore, to assess the LTP threshold in ENR and CON rats, we rather measured the number of 100-Hz stimuli required to induce LTP (see Petersen *et al*., 1998). Because it was impossible to monitor synaptic transmission during our standard 1-s-long train of 100-Hz stimulation, we performed another series of experiments during which we varied the number of stimuli within the train of 100-Hz stimulation. Figure 5B shows the effect of 5, 10, 30, 50, 70 stimuli at 100 Hz on synaptic strength in ENR ($n = 6$) and CON ($n = 6$) rats. In ENR rats, a significant potentiation was already observed after five stimuli (118.6 ± 4.3% of baseline; 30 min after HFS; Wilcoxon's signed ranks test: $z = -2.2$, $P = 0.028$). But, in CON rats, it required a minimum of 50 stimuli (124.4 ± 6.8% of baseline; $z = -2.0$, $P = 0.046$). Changes in synaptic transmission were significantly larger in ENR compared with CON rats at all train durations (one-way ANOVA: 5 stimuli, $F_{1,9} = 14.1$, $P = 0.0045$; 10 stimuli, $F_{1,10} = 15.8$, $P = 0.003$; 30 stimuli, $F_{1,10} = 26.3$, $P = 0.000$; 50 stimuli, $F_{1,10} = 14.3$, $P = 0.004$; 70 stimuli, $F_{1,10} = 8.7$, $P = 0.014$). That the number of 100-Hz stimuli required to obtain LTP was reduced in ENR rats strongly suggests that environmental enrichment decreases the threshold for LTP.

Another possible explanation for larger LTP and LTD in ENR rats compared with CON ones is an enhancement in the 'dynamic range of synaptic modification'. Rioult-Pedotti *et al*. (2000) defined the synaptic modification range using repeated LTP or LTD induction episodes until no additional synaptic change is obtained. In hippocampal CA1, four–five HFSs are usually required to reach the upper limit (see Oliet *et al*., 1997; Van Dam *et al*., 2004), and three LFSs to reach the lower limit (see Dudek & Bear, 1993) of modification. However, the last induction episodes in these series have relatively little additional effect. Therefore, to assess the dynamic range of synaptic modification in ENR and CON rats, we used a more standardized protocol, applying fixed numbers of HFSs and LFSs. We defined the lower limit as the relative value of the fEPSP slope 60 min after two LFSs (15-min-long train of 1-Hz stimulation at 15-min interval; Fig. 5C) and the upper limit as that 20 min after three HFSs (1-s-long trains of 100-Hz stimulation at 20-min interval; Fig. 6A). ENR rats, that had demonstrated larger LTD, also showed larger LTP than CON rats (238.7 ± 13.8%, $n = 5$, and 188.7 ± 12.6% of

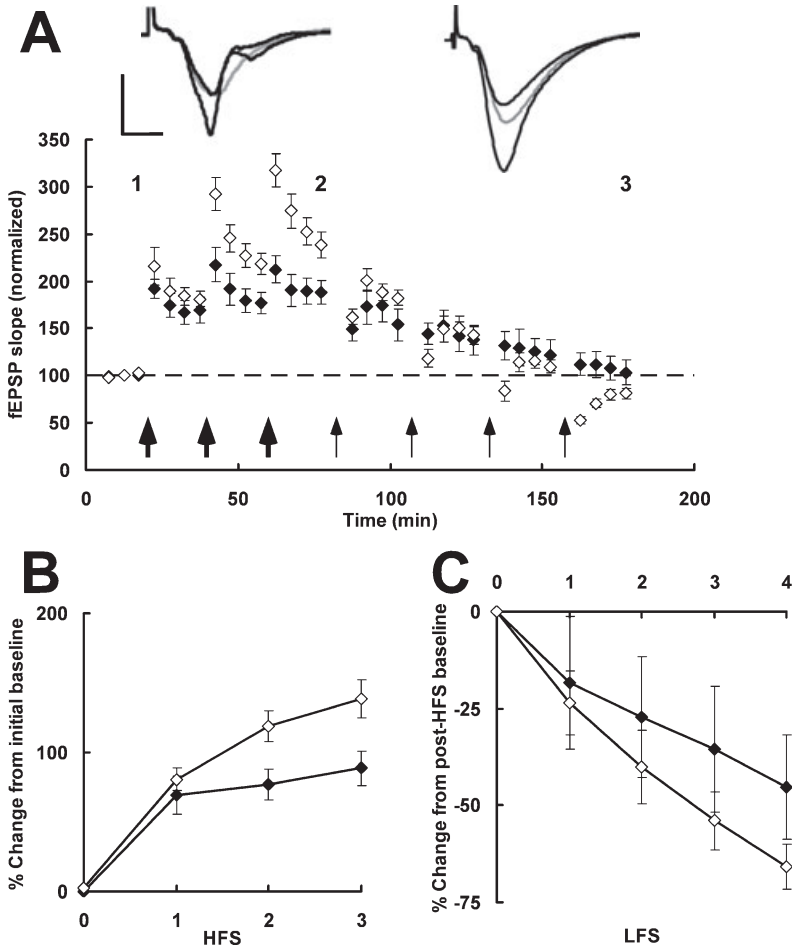

FIG. 6. Effect of environmental enrichment on the dynamic range of synaptic plasticity in hippocampal CA1 area. (A) Graph displaying the mean (± SEM) of field excitatory postsynaptic potential (fEPSP) slope over time for the two groups of rats: ENR (empty symbols; $n = 5$) and CON (filled symbols; $n = 6$) rats. High-frequency stimulation HFSs (1-s-long trains of 100-Hz stimulation) and low-frequency stimulations (LFSs) (5-min-long trains of 1-Hz stimulation) were applied (20-min intervals) at thick and thin arrows, respectively. *Inset*: Traces of 15 averaged responses (0.03 Hz) recorded at: (1) baseline (grey); (2) after repeated HFS (black); and (3) LFS (black) from slices taken from representative CON (left) and ENR (right) rats. Scale bars: 5 ms, 1 mV. (B) Plotted is the average (± SEM) cumulative effect measured 20 min after each episode of HFS in (A) as percentage of baseline fEPSP slope. (C) Plotted is the average (± SEM) cumulative effect measured 20 min after each episode of LFS in (A) as percentage of fEPSP slope after the last HFS. HFSs and LFSs induce larger changes in fEPSP slope in ENR than in CON rats. Symbols in (B) and (C) are as in (A).

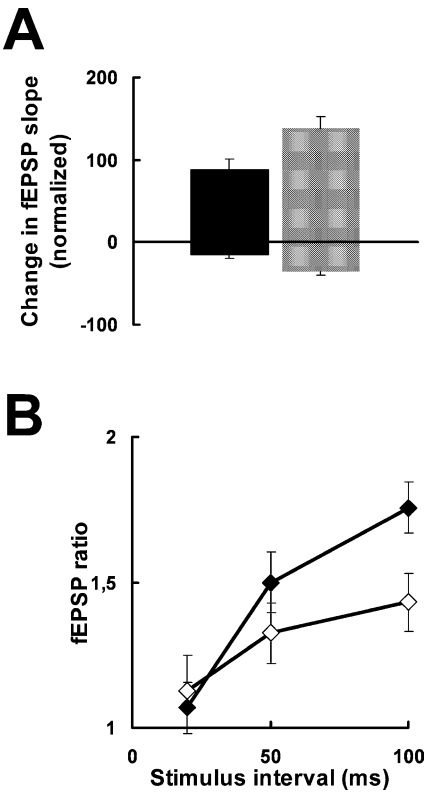

FIG. 7. (A) Bar chart summarizing the changes in mean field excitatory postsynaptic potential (fEPSP) slope (+ SEM) in CON (black) and ENR (grey) rats measured 60 min after the last LFS of two (lower limit; data from Fig. 5C) and 20 min after the last HFS of three (upper limit; data from Fig. 6A). ENR rats have a larger dynamic range of synaptic plasticity than CON ones. (B) Plot of fEPSP2/fEPSP1 ratio vs. interstimulus interval in CON (filled symbols; $n = 5$) and ENR rats (empty symbols; $n = 5$). Exposure to enriched environment decreased the fEPSP2/fEPSP1 ratio significantly ($P < 0.05$) at the longest (100 ms) interval.

baseline, $n = 6$ in ENR and CON rats, respectively; one-way ANOVA: $F_{1,9} = 24.6$, $P = 0.001$). Figure 6B shows that the second and third HFSs had a relatively larger additional effect in ENR than CON rats. The dynamic range of synaptic modification was therefore increased in ENR rats (Fig. 7A). We also tested the effect of repeated LFSs (four 5-min-long trains of 1-Hz stimulation at 20-min interval) on potentiated synapses. Again, ENR rats showed a larger depotentiation compared with CON rats (to 81.4 ± 5.8% and 103.4 ± 13.4% of pre-HFS baseline in ENR and CON rats, respectively; $F_{1,9} = 9.2$, $P = 0.014$). As for repeated HFSs, the second and subsequent LFSs had a relatively larger additional effect in ENR than CON rats (Fig. 6C).

Finally, because the induction of both LTD and LTP might be facilitated in ENR rats, we examined whether environmental enrichment had an effect on presynaptic function by measuring paired-pulse facilitation (PPF) at different interstimulus intervals (20, 50 and 100 ms). PPF is inversely correlated with the probability of transmitter release (Zucker, 1989). PPF was significantly reduced at 100 ms in ENR rats (one-way ANOVA: $F_{1,8} = 5.9$, $P = 0.041$) (Fig. 7B). This change in PPF suggests that environmental enrichment increases the probability of transmitter release.

Discussion

This study demonstrates that, in rats, two behavioural paradigms consisting of either social defeat followed by different housing conditions or environmental enrichment resulted in long-lasting changes in the induction of subsequent synaptic plasticity in hippocampal CA1. LTD was enhanced and LTP impaired several months after social defeat, whereas they were both enhanced a few weeks after 5-weeks exposure to enriched environment.

The two behavioural paradigms resulted in different changes in the induction of subsequent synaptic plasticity. It is worth noting that, first, rats exposed to each behavioural paradigm were compared with age-matched controls. Second, all electrophysiological experiments were performed in the same laboratory. Third, to assess synaptic plasticity, we initially applied the very same LFSs − though repeated in ENR and CON rats – and HFSs (see Figs 2 and 5) to the two groups of animals. Only subsequent electrophysiological tests differed to specifically address the mechanisms involved in each behavioural paradigm. We conclude that the difference in behavioural experience accounts for, at least in part, the differences in the induction of synaptic plasticity.

Social defeat followed by individual housing facilitates the induction of LTD and inhibits that of LTP

Rats exposed to either social defeat or individual housing showed a reduced degree of potentiation. Exposure to social defeat followed by individual housing (DI rats) resulted in a complete impairment of LTP and occurrence of LTD. Similar changes in the induction of hippocampal synaptic plasticity − impairment of LTP and ability to induce LTD − have been observed shortly after acute behavioural stress (Foy *et al*., 1987; Shors *et al*., 1989; Kim *et al*., 1996; Xu *et al*., 1997). That CA1 synapses in the same DI rats could nevertheless undergo LTP provided that stimulus intensity – and thus postsynaptic depolarization − during HFS was increased suggests that stress-induced impairment of LTP is due to an elevation in the threshold for inducing LTP. Such a conclusion is in agreement with previous results. First, exposure to a predator blocks primed burst potentiation, a low-threshold form of plasticity, but not HFS-induced LTP (Meshes *et al*., 1999). Second, LTP can be demonstrated in stressed animals if synapses have been previously depressed (Kim *et al*., 1996). It is known that prior depressing synaptic transmission lowers the threshold for subsequently inducing LTP (Ngezahayo *et al*., 2000). Such a shift might thus cancel the effect of stress. Therefore, our results are consistent with the hypothesis that social defeat followed by individual housing results in concomitant left- and rightward shifts in the thresholds for inducing LTD and LTP, respectively (Fig. 8A; see also Coussens *et al*., 1997; Kim & Yoon, 1998). Defeat or isolation alone would produce mild shifts manifest as only a reduction in 100-Hz-induced LTP. However, when combined, the two paradigms have a much stronger effect manifest as a complete suppression of LTP at (test intensity) 100 Hz and the occurrence of LTD at 1 Hz.

To obtain LTP in DI rats, we used a stimulation pattern in which not only stimulus intensity but also the number of trains (four 1-s-long trains of 100-Hz stimulation separated by 10 s) was enhanced. LTP is not a unitary phenomenon, but rather appears to involve early, intermediate and late phases (Frey *et al*., 1993; Huang & Kandel, 1994; Winder *et al*., 1998). Interestingly, early and late LTP can be distinguished not only by their duration but also by their induction requirements. Late LTP needs repeated trains of stimuli and is critically dependent on cAMP-dependent protein kinase A (PKA; Frey *et al*., 1993; Matthies & Reymann, 1993; Huang & Kandel, 1994), whereas early LTP induced by a single train is only partially decreased by inhibitors of the adenyl cyclase/PKA pathway (Huang & Kandel, 1994; Blitzer *et al*., 1995; Otmakhova *et al*., 2000). Therefore, a possible interpretation of our results is that social defeat and individual

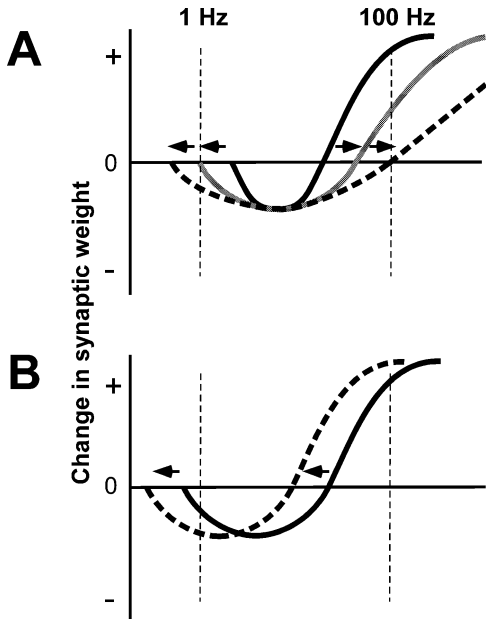

FIG. 8. Proposed changes in the synaptic plasticity induction function elicited by social stress and/or individual housing (A) and environmental enrichment (B). Curves in control conditions (black curves in A and B) are adapted from Bienenstock *et al.* (1982) and Artola & Singer (1993). Synaptic activity and associated postsynaptic responses above the basal level ($x = 0$) will induce either LTD if above the LTD threshold (θ^-), or LTP if above the LTD/LTP crossover point or LTP threshold (θ^+). The window for LTD induction (between θ^- and θ^+) in (B) is larger than that in (A) because, though all rats in this study were adult at the time of decapitation, CON rats were younger than CS ones (3–4 months vs. 1 year old). Induction of LTD with 1-Hz LFS decreases with age (see Dudek & Bear, 1993). Such age difference may account for the fact that 1-Hz LFS produced a small LTD in CON but not in CS rats (compare 1-Hz dashed line in A and B). (A) Exposure to social defeat and/or individual housing lowers the LTD threshold and concomitantly raises the LTP threshold (grey and dashed curves; direction of the change shown by arrow heads). Alone, social defeat or individual housing produces mild shifts manifest as only a reduction in 100-Hz-induced LTP (dark grey curve). Together, the two behavioural paradigms have a much stronger effect manifest as both a complete suppression of LTP at (test intensity) 100 Hz and the occurrence of LTD at 1 Hz (dashed curve) (see 1- and 100-Hz dashed lines). Similar shifts have been hypothesized to account for the effects of glucocorticoid receptor activation (Coussens *et al.*, 1997) and prior synaptic activity on synaptic plasticity (Ngezahayo *et al.*, 2000; Mockett *et al.*, 2002). This broadening of the window for LTD induction differs from the Bienenstock–Cooper–Munro (BCM, Bienenstock *et al.*, 1982) model in that the LTD threshold shifts as well as the LTD/LTP crossover point or sliding threshold (ϕ_m in the BCM model). (B) Exposure to environmental enrichment concomitantly lowers LTD and LTP thresholds (dashed curve; direction of change shown by arrowheads). Both LTP and LTD are enhanced (see 1- and 100-Hz dashed lines).

housing selectively impair early LTP induced by a single 100-Hz stimulation, but not late LTP produced by repeated trains. However, this is very unlikely. Stimulation patterns generating PKA-dependent late LTP typically involve widely spaced trains (intertrain interval $\sim$10 min: Frey *et al.*, 1993; Matthies & Reyman, 1993; Huang & Kandel, 1994). They are thus very different from the pattern − with closely spaced trains (intertrain interval = 10 s) − we used here, and LTP induced by closely spaced trains exhibits similar properties as that produced by a single HFS: it is also only partially reduced by inhibitors of PKA (Blitzer *et al.*, 1995). Therefore, we conclude that four 1-s-long trains of 100-Hz stimulation separated by 10 s induced LTP in DI rats because they produced a stronger postsynaptic activation than a single tetanus and thus reached the elevated threshold for inducing LTP.

There is growing evidence that the induction of synaptic plasticity depends on prior synaptic activity. Interestingly, activity-dependent modulation of subsequent synaptic plasticity, referred to as metaplasticity (Abraham & Bear, 1996; Abraham & Tate, 1997), is also mediated through opposite shifts in the levels of postsynaptic depolarization required for inducing subsequent LTD and LTP. In the hippocampus, for instance, prior synaptic stimulation sufficient to induce LTD lowers the threshold for the induction of subsequent LTP and, concomitantly, raises that for LTD (Ngezahayo *et al.*, 2000). On the other hand, strong synaptic activation, whether it induces LTP or no overt change in synaptic efficacy, can decrease the threshold for the induction of subsequent LTD and, simultaneously, elevate that for LTP (Barrionuevo *et al.*, 1980; Coan *et al.*, 1989; Stäubli & Lynch, 1990; Fujii *et al.*, 1991, 1996; Christie & Abraham, 1992; Huang *et al.*, 1992; Larson *et al.*, 1993; Wexler & Stanton, 1993; Bortolotto *et al.*, 1994; O'Dell & Kandel, 1994; Christie *et al.*, 1995; Wagner & Alger, 1995; Holland & Wagner, 1998; Wang *et al.*, 1998; Ngezahayo *et al.*, 2000; Mockett *et al.*, 2002). Thus, behavioural stress- and this second type of activity-induced modulation of synaptic plasticity display the very same phenomenology. Moreover, both activity- (Huang *et al.*, 1992; Fujii *et al.*, 1996; Abraham & Huggett, 1997; Mockett *et al.*, 2002; but see Wexler & Stanton, 1993) and behavioural stress-induced (Kim *et al.*, 1996) facilitation of LTD and inhibition of LTP require the activation of *N*-methyl-D-aspartate (NMDA) receptors. Therefore they might share similar expression mechanisms. However, the mechanisms of metaplasticity downstream from NMDA receptor activation remain poorly understood. Transient activation of protein kinase C (PKC) with phorbol-ester enhances LTD and suppresses LTP (Stanton, 1995; Wang *et al.*, 1998). But, PKC activation has also been shown to facilitate the persistence of LTP of population spike (Blank *et al.*, 2002).

How do social defeat and individual housing result in long-lasting facilitation of LTD and inhibition of LTP? One possibility is that they elevate basal synaptic transmission. This is very unlikely. There was no difference in baseline fEPSPs between groups of animals. Moreover, transferring rats from their home cage to a new environment produces a stress but no change in synaptic transmission (Xu *et al.*, 1997). Another possibility is related to corticosteroids. Corticosterone (in rodents) and cortisol (in humans) bind to mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) with a 10-fold difference in affinity. During 'normal' physiological conditions, when lower corticosterone concentrations occur within the hippocampus, high affinity MRs are preferably activated. On the other hand, with higher concentrations of corticosterone, both MRs and GRs will be activated (for review, see Kim & Yoon, 1998; de Kloet *et al.*, 1999). LTP is hard to obtain while LTD is robust in the presence of high corticosteroid concentration or of a selective GR agonist (Diamond *et al.*, 1992; Pavlides *et al.*, 1995, 1996; Coussens *et al.*, 1997), and a GR antagonist prevents the occurence of LTD (Xu *et al.*, 1998). Three weeks after social defeat, binding to MRs is strongly reduced while that to GRs remains unaffected (Buwalda *et al.*, 1999, 2001). Such a bias toward GRs might underlie the long-lasting inhibition of LTP and facilitation of LTD.

Environmental enrichment enlarges both LTD and LTP

Our data indicate that significant enhancement of LTP and LTD occurred in hippocampal area CA1 following 5 weeks of environmental enrichment (and 3–5 weeks of control housing). Two phenomena may contribute to this enhancement. One is a facilitation of the induction of synaptic plasticity. Our finding that PPF was

decreased in ENR rats compared with CON animals suggests that exposure to enriched environment enhances transmitter release and, thus, decreases the demand for presynaptic activation to reach the postsynaptic thresholds for inducing LTD and LTP. Accordingly, LTP induction required a smaller number of 100-Hz stimuli in ENR than in CON rats. This conclusion is also consistent with previous results showing that enriched environment enhances LTP induced by a single 100-Hz train (Duffy *et al*., 2001) but not that produced by four 100-Hz trains (Van Praag *et al*., 1999). Though we did not assess the threshold for LTD in ENR and CON rats by varying either stimulation frequency − decreasing stimulation frequency would have led to very long conditioning stimulations − or the number of 1-Hz stimuli − the degree of LTD is not linearly related to the number of stimuli in 1-Hz trains because the first 1-Hz stimuli have mainly a priming effect (Mockett *et al*., 2002) − it is very likely that enhanced LTD was also due, at least in part, to a facilitation of its induction. Thus, our results suggest that enrichment enhances synaptic changes by facilitating their induction, leading to a leftward shift of the function of synaptic plasticity vs. synaptic activation (Fig. 8B).

Environmental enrichment may also increase the dynamic range of synaptic modification. This range, between the lower limit defined using two LFSs and the upper one defined using three HFSs, was almost twice as large in ENR rats than in CON ones (Fig. 7A). We did not repeat LFS and HFS until they induce no additional synaptic change (state referred to as saturation: see Rioult-Pedotti *et al*., 2000). Therefore, we cannot totally eliminate the possibility that similar levels of potentiation and depression could have been obtained in CON and ENR rats provided that more induction protocols were applied. We consider this as very unlikely. In hippocampal CA1, saturation of LTP and LTD usually requires only one more induction episode than the three HFSs and two LFSs, respectively, used here; this last inducing protocols having very little effect (e.g. Dudek & Bear, 1993; Oliet *et al*., 1997; Van Dam *et al*., 2004). Moreover, that the third HFSs produced a larger potentiation in ENR than in CON rats (see Fig. 6B) suggests, conversely, that the difference between potentiations in ENR and CON rats would have been even larger after more than three HFSs. Interestingly, both potentiation and depression ranges were enlarged, suggesting that environmental enrichment had caused neither LTD nor LTP. This is consistent with previous studies showing no change in amplitudes of NMDA- or AMPA-receptor currents (Duffy *et al*., 2001), and in expression levels of GluR1 and GluR2/3 proteins in hippocampal membranes of spatially enriched animals (Gagne *et al*., 1998).

Environmental enrichment appears to have different effects on synaptic plasticity in hippocampal areas. Thus, in dentate gyrus, environmental enrichment has been shown to decrease (then associated with an increase in basal synaptic transmission; Green & Greenough, 1986; Foster *et al*., 1996, 2000) as well as, together with running, increase LTP (Van Praag *et al*., 1999).

Enhancement of CA1 LTP, evident after 8-week exposure to enriched environment, appears to be absent after only 2 weeks of enrichment (Duffy *et al*., 2001). We show in this study that enhancements of LTP and LTD, seen after a 5-week exposure to enrichment, were not reversed after 3–5-weeks exposure to standard housing. Thus, both occurrence and reversal of enrichment-dependent changes in synaptic plasticity might require synaptic activity. This hypothesis is consistent with another study showing that enrichment-induced decrease in dentate LTP depends on the activation of NMDA receptors (Foster *et al*., 2000). However, the time required to induce or reverse each enrichment-induced change might vary. Increased medial perforant path–dentate gyrus synaptic transmission is totally reversed following 3–4 weeks in individual cages (Green & Greenough, 1986).

Concluding remarks

Behavioural experience is known to modulate the induction of synaptic plasticity. Our results show that such modulation can persist for a long time after behavioural experiences. LTD was enhanced and LTP impaired 7–9 months after social stress, whereas LTD and LTP were both enhanced 3–5 weeks after the end of an enrichment experience. By assessing concomitant variations in LTD and LTP, we conclude that long-lasting behaviour-induced modulation of synaptic plasticity involves multiple (at least three) molecular processes. Impairment, on the one hand, and enhancement, on the other hand, of a given synaptic change, for instance LTP, are not necessarily accounted for by true reversal mechanisms.

It is now well established that exposure to social (Bodnoff *et al*., 1995; Von Frijtag *et al*., 2000) and more generally to behavioural stress (for review, see Kim & Diamond, 2002) has adverse effects on the memory function. Social stress, especially when it is followed by isolation, also alters intruder's behaviour for months: rats develop 'depression'-like, anhedonic behaviours (Koolhaas *et al*., 1997; Von Frijtag *et al*., 2000, 2002) known to coincide with cognitive deficits (Reijmers *et al*., 2001). Environmental enrichment, on the other hand, can dramatically improve the cognition capabilities of healthy animals (Fernandez-Teruel *et al*., 1997; Kempermann *et al*., 1997; Van Praag *et al*., 1999; for review, see Van Praag *et al*., 2000). Recent studies have shown that environmental stimulation also aids recovery from multiple forms of brain injury, including traumatic brain lesion (Will *et al*., 1977; Kolb & Gibb, 1991; Rose *et al*., 1993), status epilepticus (Faverjon *et al*., 2002; Rutten *et al*., 2002) and ischaemia (Farrell *et al*., 2001; Dahlqvist *et al*., 2004; Gobbo & O'Mara, 2004). Enrichment also attenuates, if not rescues, cognitive deficits associated with hippocampal deletion of NMDA receptor 1 (Rampon *et al*., 2000), ageing (Kubanis *et al*., 1982; Soffie *et al*., 1999; Frick & Fernandez, 2003) and Alzheimer's disease (Jankowsky *et al*., 2005). Interestingly, chronic stress and enrichment have also opposite effects on the sensitivity of reward systems (Von Frijtag *et al*., 2000; Van der Harst *et al*., 2003a). It is widely believed that long-term changes in synaptic transmission underlie learning and memory. Behaviour-induced variations in the thresholds for synaptic potentiation and depression might thus affect learning and memory capabilities. However, clearly, both social stress and environmental enrichment modulate other brain functions or behaviours. This raises the question as to whether such modulations involve similar synaptic mechanisms. Remarkably, the effects of social stress on, both, depressive-like behaviours and the induction of synaptic plasticity are reversed by chronic antidepressant treatment (Von Frijtag *et al*., 2001, 2002; Ramanathan *et al*., 2003).

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Abbreviations

ACSF, artificial cerebrospinal fluid; fEPSPs, field excitatory postsynaptic potentials; GR, glucocorticoid receptors; HFS, high-frequency stimulation; LFS, low-frequency stimulation; LTD, long-term depression; LTP, long-term potentiation; MR, mineralocorticoid receptors; NMDA, *N*-methyl-D-aspartate; PKA, protein kinase A; PKC, protein kinase C; PPF, paired-pulse facilitation.

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