A Conditioned Stressful Environment Causes Short-Term Metaplastic-Like Changes in the Rat Nucleus Accumbens

Sandrine Hugues, Karima Kessal, Mark J. Hunt, and René Garcia
Neurobiologie Comportementale, Equipe Avenir, Institut National de la Santé et de la Recherche Médicale, Université de Nice-Sophia Antipolis, 06108 Nice, France

Submitted 2 October 2002; accepted in final form 21 July 2003

Hugues, Sandrine, Karima Kessal, Mark J. Hunt, and René Garcia. A conditioned stressful environment causes short-term metaplastic-like changes in the rat nucleus accumbens. J Neurophysiol 90: 3224–3231, 2003; 10.1152/jn.00895.2002. Stress-related alterations to the induction of hippocampal synaptic plasticity have been implicated in certain forms of psychiatric disorders. However, relatively little is known about such changes in other psychiatric disorders-related structures. We tested this possibility in one of such structures, the nucleus accumbens, during re-exposure of rats to a conditioned stressful environment, in which they had previously received shock. In both control rats (no shock) and shocked rats previously submitted to an extensive pre-exposure to the to-be-conditioned contextual cues (latent inhibition), high- and low-frequency stimulation of fimbria-accumbens pathway induced, in the nucleus accumbens, similar pattern of increases and decreases in synaptic efficacy, respectively. However, in non–pre-exposed shocked rats, re-exposure to the conditioned contextual cues evoked high levels of freezing, which was accompanied by a blockade of the induction of enhancement, but a facilitation of the depression, of synaptic efficacy. In addition, contextual conditioning did not alter the baseline transmission whatever the stimulus intensity and was ineffective on the induction of fimbria-accumbens synaptic plasticity following complete extinction of freezing response to the conditioned contextual cues. These data support the idea according to which stress may be involved in certain forms of psychiatric disorders via induction of metaplastic changes in circuits including the hippocampus and hippocampal limbic target structures such as the nucleus accumbens.

INTRODUCTION

Psychopathological theory suggests that certain psychiatric disorders that are precipitated by stressful events (e.g., post-traumatic stress disorder and certain forms of depression) are associated with abnormalities in learning and memory mechanisms via abnormal changes in the capacity of synapses to develop plasticity (Garcia 2002a,b). However, basic studies, conducted to test the effects of stress on induction of synaptic plasticity (both increases and decreases of synaptic efficacy) have been, to date, limited on the hippocampus (Garcia 2002a). For example, as shown with artificial models of learning and memory, synaptic plasticity can develop following either high-frequency stimulation (HFS), producing an increase, or low-frequency stimulation (LFS), inducing a decrease in synaptic efficacy. As shown by various studies (for review, see Garcia 2001; Kim and Yoon 1998), stressful conditions block the HFS induction of enhancement and facilitate LFS induction of depression of hippocampal synaptic efficacy, respectively.

It has also been suggested that stress produces memory impairment (Garcia 2001, 2002a; Kim and Diamond 2002) and resumption of drug self-administration (Hyman and Malenka 2001; Winder et al. 2002) via changes in synaptic plasticity induction. The present study was therefore conducted to investigate whether the nucleus accumbens, which is involved in memory processes (Setlow 1997), addiction (Robbins and Everitt 1996), and depression (Nestler et al. 2002) also displays stress-related changes in plasticity induction. To test this, stressful conditions were obtained by re-exposing rats to a context where they had previously received shock the day before. One prediction based on hippocampal data (Garcia 2002a) is that contextual re-exposure should impair induction of synaptic plasticity (both HFS induction of enhancement and LFS induction of depression) in the nucleus accumbens. To verify this, other rats were either exposed to “no-shock condition” (experiments 1 and 2) or submitted to a latent inhibition protocol (experiment 1), which retards, because of an extensive pre-exposure to the to-be-conditioned contextual cues, contextual fear conditioning (Westbrook et al. 1997).

EXPERIMENT 1

Methods

The experiments were performed using male Wistar rats weighing between 250 and 350 g. They were individually housed in Plexiglas cages and were maintained on a free feeding regimen with a 12/12-h light/dark schedule (lights on at 7:30 AM). All behavioral studies took place during the light part of the cycle. The experiments were performed in accordance with the European Community Guidelines on the care and use of laboratory animals (86/609/EEC).

Using sodium pentobarbital (60 mg/kg, ip) anesthesia and conventional surgery techniques, rats were ipsilaterally implanted with electrodes made of twisted platinum-iridium (90–10%) wires (90 μm diam), insulated except at the tip. Electrodes were positioned in the hippocampal efferent-afferent pathway: the fimbria (stimulation: 1.3 mm posterior to bregma and 1.5 mm lateral to midline) and the nucleus accumbens (recording: 1.65 mm anterior to bregma, 0.8 mm

Address for reprint requests and other correspondence: R. Garcia, Neurobiologie Comportementale, Faculté des Sciences, Université de Nice-Sophia Antipolis, Parc Valrose, 06108 Nice, France (E-mail: rene.garcia@unice.fr).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
lateral to midline). The depth of electrodes was adjusted until a characteristic evoked field potential, as described by Boeijinga et al. (1990), was recorded. The exact placement of the electrodes was verified on completion of the experiments by standard histological methods. In addition to electrode placement in the brain, two stimulating electrodes (stainless steel wires, 110 μm diam, insulated except at the tip: 0.4–0.6 mm exposed) were inserted in the right eyelid (without altering the eyelid function) for shock administration. The entire miniature system was fixed in place onto the skull with dental cement. Subjects were allowed to recover in their home cages in the colony room for ≥5 days.

Pre-exposed animals were placed in an opaque plastic box, which was cylindrical (29 cm diam × 33 cm high) and divided by a transparent wall (23 cm side × 30 cm high) made of glass. The animal was introduced into the larger side of the box and did not have access to the other side. The floor, made of rough glass, and walls of the box were washed before and after each session with a solution containing a mixture of coconut and vanilla scent (conditioning box). A speaker placed outside the box provided a 60-dB background noise, which was part of the to-be-conditioned contextual cues. Non-pre-exposed animals were placed in a cylindrical (30 cm diam × 40 cm high) transparent Plexiglas box with a plastic floor. This second context was washed with a solution containing a mixture of ethanol (70%) and lemon scent. The 60-dB background noise was turned off.

Electrophysiological activity was recorded through JFET operational amplifiers connected to the headstage to minimize artifacts due to head movement. Cables from the junction field effect transistor (JFET) were relayed at the top of each box by a multi-channel rotating connector allowing the animals free movement within the box. Field potentials evoked in the nucleus accumbens by single-pulse stimulation (0.1-ms rectangular mono- or biphasic pulses), applied to the fimbria, were sent to an amplifier (gain 1,000; band-pass 0.001–1 kHz) and recorded (pClamp6 software, Texas Instruments) for off-line analysis. Before the first baseline recording, responses were measured as a function of stimulus strength (input-output curves: 50–800 μA).

An intensity corresponding to 60–70% of the saturation level was chosen for the test stimulus (baseline and posttrain recordings). To determine whether the excitatory P10 and P25 components of the field potential are synaptic responses or generated by cell firing in the nucleus accumbens, extracellular single-unit activity was recorded on rats (n = 4) acutely prepared under anesthesia. Stimulation of the fimbria fibers was performed as above, but with low stimulus intensities. Evoked responses in the nucleus accumbens were recorded with the use of glass microelectrodes filled with 2 M-NaCl, having tip diameters of 5–10 μM and DC resistances in saline between 1 and 5 MΩ. The responses were filtered and amplified (band-pass: 0.3–10 kHz; gain: 10,000 for unitary activity; band-pass: 0.001–1 kHz; gain: 1,000 for field potential). Recording placements were determined by the response pattern of the recorded field potential.

The behavior of each rat was continuously monitored. However, the behavior was videotaped only during the first 130 s that followed the entry of animals into the conditioning box to score freezing behavior. Freezing during the first 10 s was not scored because of the short-lasting exploration that followed the entry into the box. During the next 120 s, a rat was considered to freeze when it adopted a motionless posture, refraining from all but respiratory movements (Blanchard and Blanchard 1969). Freezing was scored using a time-sampling procedure.

Following recovery from surgery, rats were habituated to being transported (from the animal house to the experimental room) and to being connected (and disconnected) to the miniature headstage over a 3-day period (days 1–3). Each day, each animal was exposed to either the to-be-conditioned contextual cues (pre-exposed group; n = 14) or the other box (non-pre-exposed group; n = 25) for 30 min. After the 3 days of habituation, each animal continued to be exposed to its corresponding box for 3 further days (days 4, 5, and 8; 30 min/day). Baseline electrophysiological responses were established over the latter 3-day period (1 recording session/day). Animals were left undisturbed in the animal room during days 6 and 7. On day 8, 1 h after the last baseline recording, each rat was placed into the conditioning box, but only the 14 pre-exposed and 13 non-pre-exposed rats received two eyelid shocks (2 min apart) 2 min after being introduced (the remaining 12 non-pre-exposed, nonshocked, served as control animals). Each shock comprised a train of eight pulses at 5 Hz (pulse intensity: 3 mA). Sixty seconds after the second eyelid shock, all animals were returned to their home cages in the animal room for 24 h. The next day, all animals were re-exposed to the conditioning box where both freezing behavior and field potentials were recorded during the first 130 s. This protocol was chosen because freezing toward contextual cues is maximal during the first 2 min of re-exposure. Thus the first 2-min recording allowed assessment of synaptic plasticity related to conditioning. During this period, both freezing and field potentials were recorded every 30 s. This corresponded to seven field potentials at 0.2 Hz per 30-s recording block. The same electrophysiological recordings protocol (30-s recording block) was adopted for both baseline and posttrain recordings. Identical recording procedure has been found reliable in other recent studies (Herry and Garcia 2002; Herry et al. 1999). After the first 2-min recording period (re-exposure phase), each animal received either HFS (a train of 100 pulses at 100 Hz) or LFS (a train of 6,000 pulses at 4 Hz) to the fimbria. Posttrain recordings were performed 5, 10, and 15 min later.

All electrophysiological and behavioral data were expressed as means ± SE and analyzed by ANOVA.

Results

Electrode placements are shown in Fig. 1. A and B. The histological analysis revealed that all implanted rats (n = 39) had electrode placements in the lateral portion of the fimbria (stimulating sites) and in the shell region of the nucleus accumbens (recording sites).

As previously reported by Boeijinga et al. (1990), electrical stimulation of the fimbria evoked a field potential in the nucleus accumbens characterized by two positive deflections peaking at 10 and 25 ms (P10 and P25; Fig. 1C). According to Boeijinga et al. (1993), P10 and P25 are population spikes generated by monosynaptic and polysynaptic activation, respectively. Here also, single stimuli delivered to fimbria evoked single action potentials in the nucleus accumbens neurons, the latency of which coincided with the P10 component (Fig. 1C). Because P25 disappeared in certain cases after treatment (HFS or LFS), plasticity in the nucleus accumbens was assessed by changes in the amplitude of P10 (peak-to-peak from the initial negativity to P10; Fig. 2, A and B) that was clearly identifiable in all conditions.

Analyses of electrophysiological data of rats in the HFS groups (Fig. 3A) showed that the P10 population spike amplitude was stable during both baseline establishment (3 levels; F = 2.8) and from the baseline to the re-exposure phase (7 levels; F = 1.6). Moreover, there was no effect of group [pre-exposed (PE), shocked, and nonshocked non-pre-exposed (NPE and control, respectively); baseline and from baseline to re-exposure; F < 1] nor group × block interaction (baseline: F = 1.5; from baseline to re-exposure: F < 1). In other words, re-exposure to the aversive conditioned environment did not alter synaptic efficacy in the fimbria-accumbens pathway (Fig. 3A: pre-HFS). However, HFS of the fimbria, applied 130 s after the animal’s entry, produced an increase in P10 amplitude in both control and PE animals (e.g., 15 min post-HFS: 118.4 ± 3.1 and 124.4 ± 10.1% of baseline, respectively; Fig.
A, but see also Fig. 2A). On the contrary, the same stimulus parameter (100 Hz and 1 s) induced a slight tonic depression of the P10 amplitude in NPE animals (e.g., 5 and 15 min post-HFS: 90.5 ± 4.1 and 92.3 ± 5.6% of baseline, respectively). A two-way ANOVA performed on these data (6 levels: 3 baseline blocks and 3 post-HFS blocks) revealed a significant main effect of group \( F(2,16) = 13.5; P < 0.001 \), a significant main effect of block \( F(5,80) = 4.4; P = 0.001 \), and a significant interaction effect \( F(10,80) = 4.8; P < 0.0001 \). Direct between-group comparisons showed that the NPE group differed from both control and PE groups [NPE vs. control: \( F(1,10) = 21.2; P = 0.001 \); NPE vs. PE: \( F(1,12) = 18.1; P = 0.001 \)], whereas control and PE groups did not differ from each other (\( F < 1 \)). Post hoc Scheffe tests indicated that in both control and PE groups, significant enhancement of synaptic efficacy occurred at 10 and 15 min after HFS (all \( P < 0.01 \)). In contrast, changes in the NPE group were not significant at all post-HFS delays. Thus fear conditioning to novel environment blocks the capacity of fimbria HFS to enhance synaptic efficacy in the nucleus accumbens, while extensive exposure of rats to the to-be-conditioned environment inhibits such an effect.

To confirm that a given treatment has induced changes in plasticity induction, when identified with one form of synaptic plasticity, it is necessary to demonstrate that the same treatment produces also changes in the induction of the opposite form of synaptic plasticity (Abraham and Tate 1997). Therefore we also analyzed whether application of LFS, known to depress synaptic efficacy in nucleus accumbens slices (Thomas et al. 2001), would induce a decrease in nucleus accumbens synaptic efficacy in behaving rats and whether contextual fear conditioning alters this induction.

To verify this, we used identical groups of rats as previously (i.e., control, PE, and NPE). A two-factor repeated measures ANOVA indicated that amplitude of P10 was stable across the 3 days of baseline recording sessions (\( F < 1 \)) and did not differ among the three groups (group effect: \( F < 1 \); group \times block interaction: \( F < 1 \)). Twenty-four hours after shock application (PE and NPE groups), re-exposure of animals to the conditioning environment did not alter the P10 population spike amplitude (Fig. 3B: pre-LFS). A two-way ANOVA confirmed that the four re-exposure blocks did not differ from the three baseline blocks (\( F < 1 \)), with no effect of group (\( F < 1 \)) or

![FIG. 1.](gb) Diagrams of coronal sections of the rat brain showing electrode placements (dotted areas) in the lateral fimbria (A) and the shell region of the nucleus accumbens (B: AcbSh). ac, anterior commissure; AcbC, core region of the nucleus accumbens; cc, corpus callosum; ic, internal capsule. C: examples of field potential (top) and single-unit activity (bottom) evoked in the nucleus accumbens following stimulation of fimbria. Latency of evoked single-unit activity \((\Delta)\) coincided with peak latency of the P10 component of the field potential. Single-unit activity recorded at the P25 latency (**) was probably spontaneously generated (see also *). S, stimulus artifact.

![FIG. 2.](gb) A and B: examples of largest changes in synaptic efficacy in the nucleus accumbens [A: following high-frequency stimulation (HFS) in a control rat; B: following low-frequency stimulation (LFS) in a non–pre-exposed rat]. Although in these examples the 2 positive components (P10 and P25) showed remarkable changes in amplitude, synaptic plasticity was evaluated only with changes occurring between the 1st negativity and the P10 peak (i.e., between the 2 dotted lines). S, stimulus artifact.
group × block interaction ($F < 1$). However, LFS of the fimbria, applied 130 s after the animal’s entry, resulted in a decrease in P10 amplitude in all rats, with a larger decrease in NPE animals (Fig. 3B; see also Fig. 2C) than in both control and PE animals. A two-way ANOVA with recording blocks (6 levels: 3 baseline blocks and 3 post-LFS blocks) indicated both significant main effects of group [$F(2,17) = 4.8; P = 0.005$] and block [$F(5,85) = 27.5; P < 0.0001$] and a significant group × block interaction [$F(10,85) = 3.6; P = 0.0005$]. Direct between-group comparisons revealed that the NPE group differed from both control and PE groups [NPE vs. control: $F(1,11) = 9.1; P = 0.01$; NPE vs. PE: $F(1,11) = 5.7; P < 0.05$], whereas control and PE groups did not differ from each other ($F < 1$). Post hoc Scheffé tests indicated that significant decrease in synaptic efficacy occurred for all groups ($P < 0.05$ for both control and PE groups; NPE group: $P < 0.0001$) at 5- and 10-min post-LFS delays. At the 15-min post-LFS delay, significant changes were observed only for the NPE group ($P < 0.0001$).

We finally evaluated freezing behavior recorded during the first part of contextual re-exposure phase (i.e., during the 120-s period preceding HFS or LFS of the fimbria). Since rats in each experiment (HFS and LFS) were treated similarly according to their group (control, PE or NPE), freezing data were combined before HFS or LFS (e.g., PE-HFS and PE-LFS) to form single mean value for each block (Fig. 4). Control rats displayed low levels of freezing across the four 30-s recording blocks. However, animals in both PE and NPE groups exhibited high levels of freezing during this period with the highest levels obtained with the NPE group. A two-way ANOVA of these data revealed a significant effect of group [$F(2,36) = 12.1; P < 0.0001$], as well as a significant effect of block [$F(3,108) = 3.6; P = 0.01$] and a significant group × block interaction [$F(6,108) = 3.1; P < 0.01$]. Direct between-group comparisons showed that control rats differed from both PE and NPE animals [control vs. PE: $F(1,24) = 4.6; P < 0.05$; control vs. NPE: $F(1,23) = 41.9; P < 0.0001$]. The same analysis indicated that the two groups of animals that received shock (PE and NPE) also differed from each other [$F(1,25) = 6.1; P < 0.05$]. However, post hoc Fisher tests revealed that these two groups did not differ from each other during the last 30-s recording block ($P = 0.27$). These analyses showed 1) that PE animals developed latent inhibition of contextual fear conditioning (low level of fear acquisition) and 2) that just before
A significant main effect of group \( [F(2,28) = 9.1; P < 0.01] \), with a significant main effect of block \( [F(9,162) = 2.2; P < 0.05] \). The interaction between group and block was also significant \( [F(9,162) = 2.4; P < 0.05] \). Post hoc Scheffe analyses}

...showed that nonshocked rats differed from shocked animals only from blocks 1 to 6 \( (P < 0.05) \).

Electrophysiological analyses indicated that the P10 component of the fimbria-accumbens field potential was stable for all intensities used \( (100, 200, 400, \text{ and } 800 \mu A) \) during the two sessions of baseline \( (F < 1) \). Stress associated with re-exposure to a conditioned aversive environment did not affect this stability at all intensities \( (\text{Figs. 6 and 7}) \). This was confirmed by statistical analyses, which indicated the absence of difference between the two groups (nonshocked and shocked animals) and no effect of block (both \( F < 1 \)).

Whatever the group, HFS, applied to the fimbria, did not also alter the amplitude of the P10 component at the 5-min posttrain delay. However, this train of stimulation produced an intensity-dependent potentiation (with higher effect at high intensities) that was revealed at the 45-min posttrain delay in both groups (nonshocked and shocked). Statistical analysis on these data did not reveal any effect of group at all intensities. A main effect of blocks was observed only at the highest intensities \[ 400\mu A: F(3,24) = 3.3; \ 800 \mu A: F(3,24) = 4.4; \text{ both } P < 0.05 \] without any interaction between group and block.

Application of LFS in the fimbria-accumbens pathway did not virtually affect transmission in this pathway at low intensities \( (100 \text{ and } 200 \mu A) \), whatever the group. However, LFS induced short- and long-lasting decreases in the P10 amplitude at 400 and 800 \( \mu A \), respectively. A two-way ANOVA at each intensity confirmed the effect of LFS only at 400 \( \mu A \) \[ F(3,24) = 3.5; P < 0.05 \] and 800 \( \mu A \) \[ F(3,24) = 5.3; P < 0.01 \]. Post hoc Scheffe tests indicated that the depression was significant \( (P < 0.05) \) in both groups (nonshocked and shocked rats) only at the shortest post-LFS delay \( (i.e., \ 5 \text{ min}) \) with 400-\( \mu A \) intensity and at both 5- and 45-min post-LFS delays with 800-\( \mu A \) intensity. The two groups did not differ from each other.

**DISCUSSION**

Modifications in synaptic responsiveness to plasticity-inducing stimulation, also known as metaplasticity \( (\text{Abraham and Bear } 1996) \), have been hypothesized to be involved in learning and memory \( (\text{Abraham } 1999) \), drug addiction \( (\text{Hyman and Malenka } 2001) \), and depression \( (\text{Garcia } 2002a) \). We show here...
for the first time that this phenomenon, widely described in the hippocampus (Garcia 2001; Kim and Yoon 1998), also takes place in another learning and memory-, addiction-, and depression-related structure, the nucleus accumbens. This was clearly demonstrated by the absence of HFS-associated enhancement, and the greater LFS-associated depression, of synaptic efficacy during the first minutes of rats’ re-exposure to conditioned aversive contextual cues.

Our data resemble the hippocampal metaplasticity phenomenon in two main respects. First, hippocampal metaplasticity occurs in certain circumstances (e.g., stress) that alter neuronal/synaptic function without affecting glutamatergic transmission (Abraham and Tate 1997). Here, despite high levels of conditioned freezing observed at the beginning of contextual re-exposure in rats experiencing contextual fear conditioning, there were no changes in glutamatergic transmission in the nucleus accumbens. This electrophysiological result is also in accordance with neurochemical data showing that re-exposure...
of rats to an environment where they had initially received foot shock does not cause changes in extraneuronal levels of glutamate in the nucleus accumbens (Saulskaya and Marsden 1995). Second, to be electrophysiologically revealed, metaplasticity requires induction, via HFS and LFS, of traditional activity-dependent synaptic plasticity [long-term potentiation (LTP) and long-term depression (LTD)]. Either an inhibition of LTP (and concomitant facilitation of LTD) or a facilitation of LTP (with concomitant inhibition of LTD) allows then to identify this phenomenon. Whereas in the first experiment, we did not monitor posttrain changes \(\leq 45\) min as in other studies examining nucleus accumbens LTP (Boeijinga et al. 1993; Mulder et al. 1998) and LTD (Robbe et al. 2002; Thomas et al. 2001), our findings reveal substantial changes in induction of plasticity under stressful conditions. Specifically, stress, due to re-exposure to conditioned aversive environment, inhibits HFS-induction of synaptic efficacy enhancement in the fimbria-accumbens pathway. Although these data replicate findings reported for the fimbria-septal (Garcia et al. 1997) and fimbria-CA3 (Garcia et al. 1998) circuits, they demonstrate the short-term aspect of this alteration.

Moreover, we observed that the inhibitory effect of stress on fimbria-accumbens synaptic efficacy enhancement was also associated with a facilitation of LFS induction of depression, as shown in hippocampal circuit in rats experiencing a stressful environment (Xu et al. 1997). This facilitatory effect was also transient; it was abolished following a complete extinction of freezing behavior. However, since animals submitted to the latent inhibition protocol displayed normal plasticity while they had significant levels of freezing at a time of synaptic plasticity induction, we suggest that changes in induction of synaptic plasticity observed in non-pre-exposed shocked animals did not result from animals’ behavioral state during re-exposure to contextual cues (i.e., freezing). Changes observed in synaptic plasticity induction could probably be due to accumbens higher processing of aversive contextual information at the beginning of contextual exposure than to expression of conditioned fear responses. Indeed, other studies suggest that the nucleus accumbens is more implicated in processing of contextual information (Fanselow 2000; Westbrook et al. 1997) than in expression of contextual conditioning (Haralambous and Westbrook 1999). Together, these data show that processing of aversive contextual information does not affect basal glutamatergic transmission but produces changes in induction of plasticity within the nucleus accumbens (i.e., a stress-related metaplasticity-like phenomenon). However, despite these common points between nucleus accumbens data and the well-described hippocampal metaplasticity (Abraham 1999; Abraham and Tate 1997), different mechanisms may govern them.

Theoretically, between HFS-inducing LTP and LFS-inducing LTD, there is an intermediate frequency where no lasting synaptic plasticity occurs (Bienenstock et al. 1982). This frequency is not fixed, but “slides” (shifts) under certain circumstances such as stress (Kim and Yoon 1998). According to the original theory, known as the Bienenstock-Cooper-Munro model (BCM theory) (Bienenstock et al. 1982), metaplasticity is due to this “sliding” effect (with, for instance, inhibition of LTP and concomitant facilitation of LTD). Contrary to the hippocampal metaplasticity, which bears some similarity with the BCM theory, changes in plasticity induction in the nucleus accumbens could simply reflect over expression of receptors mediating one form of posttrain depression. Indeed, synapses in the nucleus accumbens exhibit multiple forms of posttrain depression, each depending on a specific subgroup of glutamate receptors (Winder et al. 2002). In addition, in normal conditions, nucleus accumbens synapses may respond to both HFS and LFS with a mixture of LTP and LTD (Winder et al. 2002), the balance between both components (potentiation and depression) determining the output plasticity. This was characterized in our study by post-HFS potentiation and post-LFS depression. However, during processing of aversive contextual information, levels of posttrain depression could have increased, probably via activation of group II metabotropic glutamate receptors (mGluR) (Winder et al. 2002), without alteration in levels of potentiation. This could result in the final output plasticity observed here (i.e., slight and nonsignificant post-HFS depression and larger post-LFS depression).

Taking into account the role of the nucleus accumbens in drug addiction (Fasano and Brambilla 2002; Hyman and Malenka 2001; Winder et al. 2002) and depressive disorder (Nestler et al. 2002), we propose two potential clinical implications of the present data. First, addiction is associated with synaptic plasticity in the nucleus accumbens drug reward circuit that persists long after cessation of drug intake, predisposing individuals to high risk of relapse (Hyman and Malenka 2001). The fact that stress can precipitate relapse suggests that combination of this synaptic predisposition with stress-related metaplastic-like changes may re-establish addiction. Second, stressful events seem to precipitate depressive disorder only when their synaptic consequences in certain structures are associated with already existing synaptic plasticity (synaptic predisposition), mainly in vulnerable individuals (Garcia 2002b). In other words, the combination of nucleus accumbens synaptic predisposition with stress-related metaplastic-like changes (corresponding probably to up-regulation of group II mGluR) may be one of key mechanisms provoking relapse to drug use, and in other cases, development of depressive disorder.
DISCLOSURES

This study was supported by the Institut National de la Santé et de la Recherche Médicale (Equipe Avenir).

REFERENCES

Herry C and Garcia R. Prefrontal cortex long-term potentiation, but not long-term depression, is associated with the maintenance of extinction of learned fear in mice. J Neurosci 22: 577–583, 2002.