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Distinct modulatory effects of sleep on the maintenance of hippocampal and medial prefrontal cortex LTP

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Abstract

Both human and animal studies support the idea that memory consolidation of waking experiences occurs during sleep. In experimental models, rapid-eye-movement (REM) sleep has been shown to be necessary for cortical synaptic plasticity and for the acquisition of spatial and nonspatial memory. Because the hippocampus and medial prefrontal cortex (mPFC) play distinct and important roles in memory processing, we sought to determine the role of sleep in the maintenance of long-term potentiation (LTP) in the dentate gyrus (DG) and mPFC of freely behaving rats. Animals were implanted with stimulating and recording electrodes, either in the medial perforant path and DG or CA1 and mPFC, for the recording of field potentials. Following baseline recordings, LTP was induced and the animals were assigned to three different groups: REM sleep-deprived (REMD), total sleep-deprived (TSD) and control which were allowed to sleep (SLEEP). The deprivation protocol lasted for 4 h and the recordings were made during the first hour and at 5, 24 and 48 h following LTP induction. Our results show that REMD impaired the maintenance of late-phase (48-h) LTP in the DG, whereas it enhanced it in the mPFC. Sleep, therefore, could have distinct effects on the consolidation of different forms of memory.

Introduction

Numerous studies have suggested that declarative or explicit memories in humans and animals undergo a first stage of processing in the hippocampus before being permanently stored in the neocortex (for review see Squire, 1992). Furthermore, several lines of evidence indicate that information acquired during wakefulness could be preferentially processed during reduced sensory input states, e.g. in sleep (Pavlides & Winson, 1989; Wilson & McNaughton, 1994; Poe *et al*., 2000; Louie & Wilson, 2001; for a recent review, see Benington & Frank, 2003). Rodents subjected to various learning paradigms (e.g. spatial maze tasks, enriched environments) also show an increase in the amount of time spent in rapid-eye-movement (REM) sleep following training (Lucero, 1970; Fishbein *et al*., 1974; Smith, 1996; Datta, 2000). This enhancement of REM sleep occurs at specific time intervals ('REM windows') after the task and is required for long-term learning (Hennevin *et al*., 1995; Smith, 1996). Different studies have also shown deleterious effects of long-term as well as short-term sleep deprivation on memory, using different learning tasks and sleep deprivation methods (Oniani, 1982; Smith, 1985). In particular, REM sleep deprivation (REMD) appears to be effective in producing learning impairments only when applied at particular 'REM windows' after training. Outside these windows, sleep deprivation has been shown to be ineffective (Smith, 1996).

Long-term potentiation (LTP) is a model of learning and memory (Bliss & Lomo, 1973); it can last hours to weeks and is modulated by the animal's behavioural state (Barnes, 1979; Bramham & Srebro, 1989; Bramham *et al*., 1994). Together with the hippocampus, the medial prefrontal cortex (mPFC) is required for spatial tasks involving working memory (Kesner & Beers, 1988). Anatomical and electrophysiological studies have demonstrated the existence of monosynaptic projections from the caudal hippocampus to the mPFC (Swanson, 1981; Ferino *et al*., 1987; Jay & Witter, 1991; Conde *et al*., 1995). These inputs have also been shown to undergo LTP and long-term depression (LTD) *in vivo* (Laroche *et al*., 1990; Jay *et al*., 1996; Takita *et al*., 1999).

LTP has only recently been used as a means of investigating effects of sleep deprivation on synaptic plasticity. A number of studies have shown that long-term (12–72 h) sleep deprivation alters the intrinsic membrane properties of hippocampal neurons and impairs LTP, recorded in the CA1 and dentate gyrus (DG), *in vitro* (Campbell *et al*., 2002; Davis *et al*., 2003; McDermott *et al*., 2003). The present study was an attempt to extend these findings on a number of points. First, recordings were performed in freely behaving animals and a short-term (4 h) sleep deprivation paradigm was used with a gentle handling method of sleep deprivation to minimize stress to the animals; both stress and the associated elevations in adrenal steroids are known to alter neuronal excitability and to suppress LTP (Diamond *et al*., 1990; Shors *et al*., 1990; Kerr *et al*., 1991; Diamond *et al*., 1992; Pavlides & McEwen, 1999; Rocher *et al*., 2004; for review see Kim & Diamond, 2002; Pavlides *et al*., 2002; Karst & Joels, 2003). Second, experiments were performed on two major pathways involved in spatial memory processing: the cortico-hippocampal projection, from the medial perforant path (mPP) to the DG, and the hippocampo–cortical projection, from the CA1 to the mPFC. Third, thus far only the induction phase of LTP was investigated, whereas the role of sleep on the long-term maintenance of LTP, which may be of greater significance for the consolidation of memory, has not yet been studied. Besides determining effects of sleep deprivation on the

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induction of LTP, we also investigated the effects of sleep deprivation on late-phase LTP. The results show that 4 h REMD suppressed the late-phase (48 h) LTP in the hippocampus but enhanced it in the mPFC.

Materials and methods

Subjects

Fifty-five male Sprague-Dawley rats (300–400 g) were housed individually in standard rodent cages in a vivarium maintained at 24 °C, and with a light : 12 h dark cycle, lights on at 07.00 h. Food and water were available *ad libitum* during all phases of the experiment. The animals were handled daily for at least 3 days before the surgery for electrode implantation. All procedures were performed according to NIH guidelines for animal research (Guide for the Care & Use of Laboratory Animals, NRC, 1996) and approved by the IACUC committee at The Rockefeller University.

Surgery

Animals were implanted with chronic recording electrodes either in the DG or the mPFC, in addition to stimulating electrodes in the mPP and CA1 for the recording of field potentials and EEG (Fig. 1). Tungsten electrodes (cross-section diameter, 100 μm) were implanted bilaterally in all animals under deep sodium pentobarbital (Nembutal®; 50 mg/kg, i.p.; Abbot Laboratories, IL, USA) anaesthesia. Briefly, the animals were placed in a stereotaxic frame and the skull was exposed and cleaned. The electrodes were lowered into the brain through holes made in the skull at the following coordinates: mPP, 7.9 mm posterior to bregma, 4.1 mm lateral to midline and

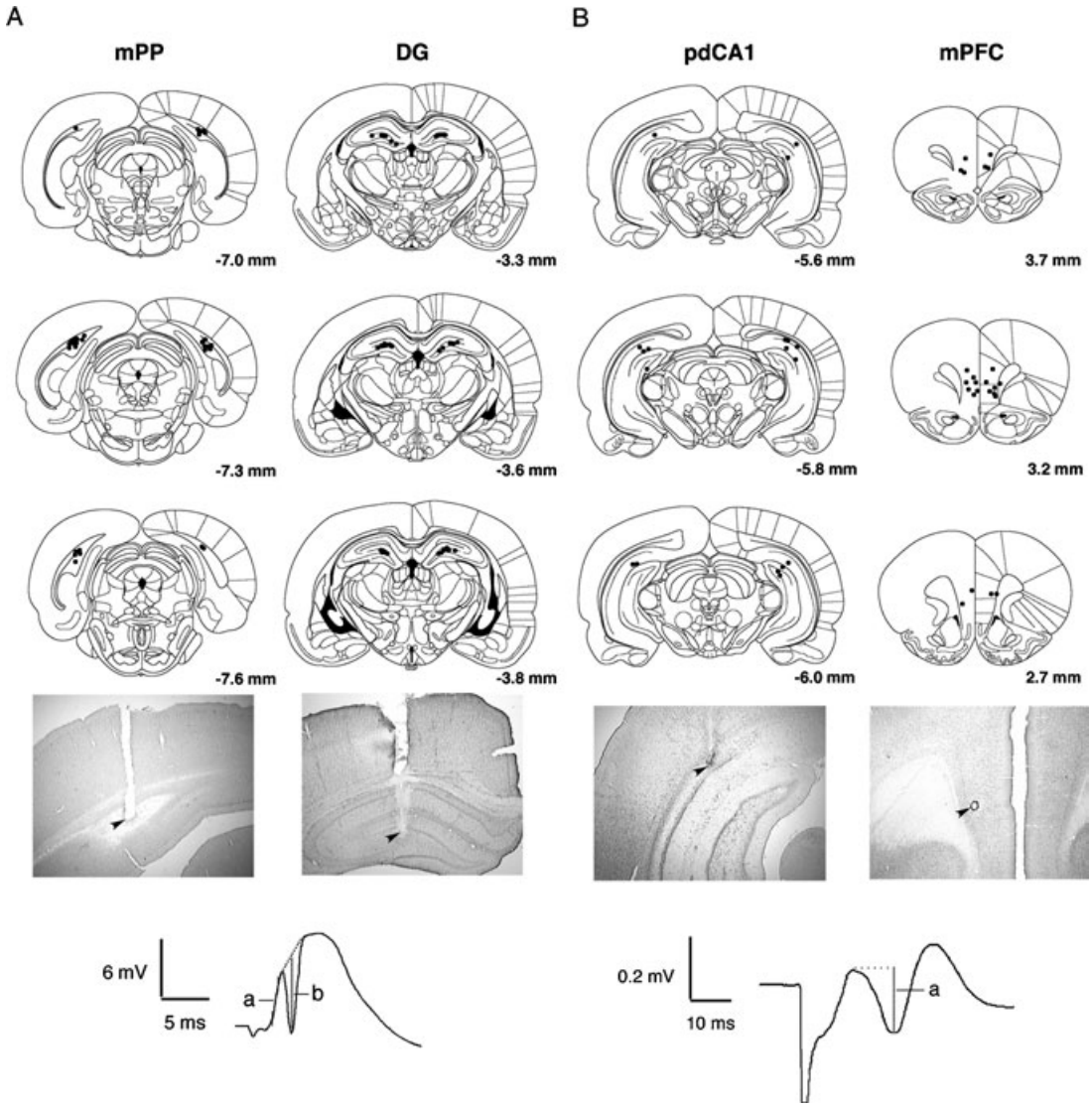

FIG. 1. Histological sections showing placement of stimulating and recording electrodes along with representative field potentials. (A) mPP–DG: electrodes were implanted bilaterally in the mPP for stimulation and DG for recording. Representative electrode positions are shown (black dots) together with histological sections of the angular bundle and DG (arrowhead). Bottom, characteristic mPP–DG evoked response indicating where the fEPSP measurements, slope (a) and population spike (b), were taken. (B) CA1–mPFC: bilateral implants in the CA1 for stimulation and mPFC for recording are depicted as black dots. The histological section indicates the position of the two electrodes. Bottom, characteristic CA1–mPFC evoked response indicating where the amplitude (a) of the PSP measurement was taken. The average PSP latency to the negative peak observed in our recordings (20.4 ± 0.3 ms) is consistent with CA1–mPFC monosynaptic projections. Antero-posterior stereotaxic coordinates are given in mm in relation to bregma (Paxinos & Watson, 1997).

3.0 mm ventral to dura mater; DG, 3.7 mm posterior to bregma, 2.1 mm lateral to midline and 3.3 mm ventral to dura mater; CA1, 6.0 mm posterior to bregma, 4.6 mm lateral to midline and 3.2 mm ventral to dura mater; and mPFC, 2.8 mm anterior to bregma, 0.6 mm lateral to midline and 3.5 mm ventral to dura mater, according to Paxinos & Watson (1997). The final positions of the electrodes in the DG were determined by audio monitoring of unit firing and recording of evoked responses elicited after test stimulations of the mPP (80 μA, 250 μs, 0.05 Hz). A similar procedure was used for the CA1–mPFC projection (test pulse 150 μA, 200 μs, 0.05 Hz). A depth profile was taken for each animal by first positioning the stimulating electrode in the CA1 pyramidal layer and moving the recording electrode through the mPFC to obtain the highest negative-going response in the mPFC. The responses obtained had to have a latency of the negative peak in the range of 18–22 ms (Laroche *et al*., 1990) and an amplitude of at least 300–400 μA. One screw positioned on the frontal bone served as reference for recording and a second above the parietal cortex served as the stimulus indifferent. The electrodes were assembled in a connector, which was cemented to the skull. All animals were allowed at least 5 days to recover from surgery before the experiment started. On each of the recovery days, they were allowed to have full sleep cycles inside the recording chamber during the lights-on period.

Hippocampal and cortical recordings

All recordings were performed in a chamber, which consisted of a wooden box (45 × 45 × 80 cm) and was illuminated by a light (2 lux floor light intensity). A small fan fixed to one side of the chamber provided both ventilation and constant low intensity white noise to muffle external sounds. The chamber was completely enclosed, and viewing of the animals was accomplished by means of two one-way mirrors set up on two of the chamber walls. Evoked responses elicited in the DG following mPP stimulation or in the mPFC following CA1 stimulation were first recorded in both hemispheres of all animals during the 2 days preceding the LTP–sleep deprivation protocol. Monophasic test pulses of 250 μs (mPP–DG) or 200 μs (CA1–mPFC) were delivered every 20 s at increasing intensities (20–300 μA). Field excitatory postsynaptic potential (fEPSP) slope and population spike in the DG, and postsynaptic potential (PSP) amplitude in the mPFC, were calculated by averaging four responses per stimulus intensity and then used to plot input–output curves for each brain hemisphere for all animals. On experimental days, the animals were placed in the recording chamber at ≈ 10.00 hours and left for 10 min, after which baseline (BL) recordings were taken bilaterally for 30 min. Ipsi- and contralateral evoked responses were simultaneously recorded following unilateral stimulation. Test stimulation was set at half maximum intensity calculated from the fEPSP slope (DG) and PSP amplitude (mPFC) input–output curves and was applied every 20 s. LTP was then unilaterally induced by applying high frequency stimulation (HFS) to the mPP or CA1. For the mPP–DG projection, HFS consisted of 10 trains (50 ms duration) of 20 pulses at 400 Hz, every 10 s. In the CA1–mPFC projection, LTP was induced using two series of 10 trains (200 ms duration), of 50 pulses at 250 Hz, 10 min apart. The hemisphere to be tetanized was randomized between animals. After LTP, ipsi- and contralateral potentials were monitored simultaneously while alternating stimulation to each hemisphere every 10 min for a total of 1 h (30 min each side). After that, the animals were either allowed to sleep or were sleep-deprived in the following 4-h period. In order to characterize the LTP decay pattern, evoked responses were recorded immediately after sleep or sleep deprivation (≈ 17.00 hours), at 24 h (11.00 hours) and 48 h (11.00 hours) after

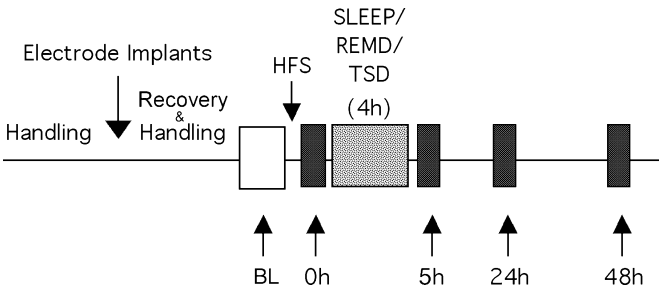

FIG. 2. Experimental paradigm. The animals were extensively handled and habituated before tetanization. Hippocampal and cortical field potentials were bilaterally recorded during BL, followed by unilateral HFS. Evoked responses were recorded immediately after LTP (0 h), after sleep or sleep deprivation (5 h), and at 24 h and 48 h after LTP induction, and were compared to BL.

HFS, for 15 min (every 20 s) from each brain hemisphere (Fig. 2). Evoked responses from the contralateral hemispheres (non-HFS side) were also systematically recorded during the experiment. Animals with unstable recordings in the contralateral side were excluded from the final analysis. It should be noted that HFS did not induce epileptic after-discharges in any of the animals included in the final analysis. All recordings were made while the animals were in a quiet awake (AW) state (based on EEG and observation of the animal's behaviour). Special care was taken to avoid recording evoked responses during drowsiness, as it has been previously shown that hippocampal field potentials vary with the animal's behavioural state (Winson & Abzug, 1977; Bramham & Srebro, 1989). This is also true for the CA1–mPFC responses (our recent unpublished observations).

Sleep and sleep deprivation

EEG (400 Hz sampling rate; 0.1–50 Hz band-pass filter) and video recordings (3 frames/s) were used to characterize sleep stages during the 4-h period following HFS. The animals were sleep-deprived by gentle handling (scratching, tapping, moving) of the recording chamber. For REM sleep deprivation, the animals were woken every time theta oscillations (5–9 Hz) were observed for 2–4 s in their hippocampal EEG along with loss of nuchal muscle tonus and/or whisker twitches following a slow-wave sleep (SWS) episode. For animals with cortical recordings, characteristic sleep spindles (10–15 Hz) observed at the transition from SWS to REM sleep and part of the intermediate stage of sleep (IS) (Gottesmann, 1996; Mandile *et al*., 1996) were used to indicate a possible REM episode to come. At this point, the animals were woken up only if they fully relaxed their head, by leaning it on the floor of the chamber or against its walls. The IS–REM sleep transition was usually characterized by the waning of sleep spindles, muscle relaxation and a clear desynchronization of the cortical EEG. IS in the absence of muscle relaxation was not considered REM sleep. EEG desynchronization following IS was also present in IS–AW transitions. In such cases, they were easily identified as the animals moved to a different sleeping position or engaged in grooming or exploration. Total sleep deprivation was achieved by waking the animals every time they were in a quiescent state, usually with eyes closed, associated with 2–4 s of high amplitude (> 200 μV) delta waves (1–4 Hz) in their hippocampal EEG. Two trained experimenters carried out all experiments. mPP–DG animals were assigned to one of three groups: sleep (SLEEP), REMD and total sleep deprivation (TSD). CA1–mPFC animals were assigned to two groups: SLEEP and REMD. The time spent in each sleep stage was quantified by off-line analysis of the EEG and video

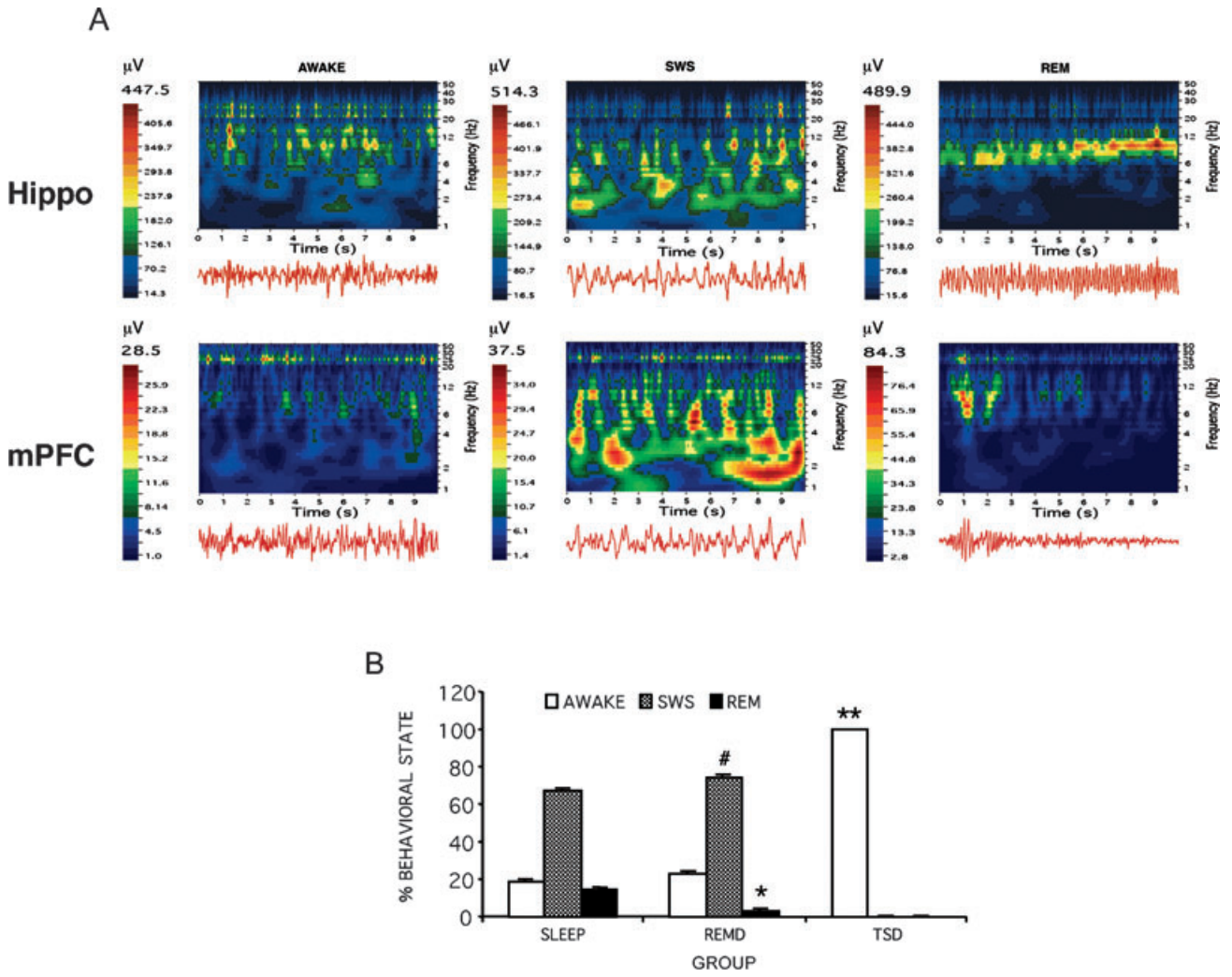

FIG. 3. Quantification of behavioural states during 4 h of sleep, REMD or TSD. (A) Time–frequency power spectrum of a 10-s epoch of hippocampal EEG, representative of the main behavioural states. The typical spectrum of the AW state consisted of high power at high frequencies (> 6 Hz), usually of low amplitude, whereas SWS was characterized by the predominance of low frequency oscillations (1–4 Hz) of high amplitude. During REM sleep, the spectral composition of the hippocampal EEG consisted of a strong 5–9 Hz oscillation (theta waves) while, in the mPFC, 11–15 Hz spindles preceded a desynchronized EEG during muscle atonia and body twitches. Typical EEG traces are shown below for each behaviour. Behavioural states were assigned based on the EEG frequency spectrum and visual observation of the animals. (B) SLEEP animals had normal sleep cycles including SWS and REM sleep. REMD animals were allowed to have SWS but were deprived of REM sleep, except for very brief SWS–REM transition bouts. The total time the animals spent in REM sleep was significantly reduced in REMD compared to SLEEP animals. TSD animals had no SWS or REM sleep. Unpaired two-tailed *t*-test. $P < 0.05$ (*, ** and $^{\#}$), compared to SLEEP group.

recordings, using objective criteria as described above. EEG segments were assigned to AW, SWS or REM sleep based on their power spectrum at 1–4 Hz (delta band), 5–9 Hz (theta band), 11–15 Hz (sigma band) and 25–45 Hz (gamma band) associated with the behavioural state of the animal (quiescence or active; Fig. 3A).

Blood sampling procedure and corticosterone assay

To determine the level of stress induced by sleep deprivation, plasma corticosterone (CORT) concentration was determined in three separate groups of animals exposed to the same paradigm as the original animals. The use of different groups was necessary to prevent the substantial amount of stress related to blood sampling on the animals in which LTP was monitored. This could have affected the LTP results. The animals were implanted with electrodes and subjected to the same habituation procedures [5 days post-surgery, 10 min in the recording chamber before BL recordings for 1 h (30 min for each hemisphere)] and either sleep or sleep deprivation for 4 h. Immediately after 4 h of sleep or sleep deprivation (REMD or TSD), the animals were anaesthetized with pentobarbital (Nembutal®; 50 mg/kg, i.p.) and blood samples were collected 10 min later from the heart. The samples were subsequently stored at −20 °C. Plasma corticosterone concentrations were determined by radioimmunoassay using a commercial kit (Coat-a-Count; Diagnostic Products Corporation, Los Angeles, CA, USA).

Statistics

Measurements are given as mean ± SEM. The relative amount of time the animals spent in each behavioural state (AW, SWS and REM sleep) was analysed using unpaired two-tailed *t*-tests. LTP induction levels in the DG and mPFC were analysed using one-way ANOVA and *t*-test, respectively. The decay of LTP over four different time points (0, 5, 24 and 48 h) was analysed using one-way ANOVA for repeated measures.

Plasma CORT levels were analysed using one-way ANOVA. Newman–Keuls *post hoc* tests were used for pair-wise comparisons whenever necessary, following ANOVA. Significance level was set to $P < 0.05$.

Results

Sleep deprivation

As expected, the sleep deprivation protocol resulted in a significant decrease in the amount of time the animals spent in each sleep state (Fig. 3B). Animals in the REMD group had significantly less REM sleep than animals in the SLEEP group (3.0 ± 0.6 vs. 14.4 ± 1.1%; $t_{29} = 9.1$, $P < 0.001$), without affecting their total sleep time (76.6 ± 1.8% REMD vs. 81.0 ± 1.7% SLEEP; $t_{29} = 1.8$, $P > 0.05$). No reduction in SWS time was observed resulting from REMD. Rather, REMD animals spent more time in SWS than SLEEP animals (74.5 ± 1.7% REMD vs. 66.6 ± 1.6% SLEEP; $t_{29} = 3.2$, $P < 0.01$). TSD animals were fully deprived of SWS and REM sleep. Drowsiness and sharp waves in the EEG of TSD animals were common, but always interrupted by gently tapping or moving the recording chamber.

Dentate gyrus

Following tetanization of the mPP–DG projection, evoked responses were recorded from the DG at four time points: 0 h (immediately after HFS), 5 h (immediately after either 4 h sleep or sleep deprivation), 24 h and 48 h after LTP induction. Figure 4 shows the time course of the fEPSP slope and population spike LTP recorded from SLEEP, REMD and TSD animals.

For both the fEPSP slope and the population spike, LTP was induced (at 0 h) to similar levels in all groups (fEPSP slope: SLEEP, 24.0 ± 2.9%; REMD, 21.8 ± 5.3%; TSD, 16.4 ± 4.0%; $F_{2,20} = 0.89$, $P > 0.05$; population spike: SLEEP, 388.9 ± 57.1%; REMD, 359.9 ± 63.2%; TSD, 263.1 ± 54.7%; $F_{2,25} = 0.86$, $P > 0.05$). A similar degree of potentiation before the deprivation paradigm was a necessary requisite for comparing LTP decay curves between sleep-deprived and non-sleep-deprived animals. One-way ANOVA for repeated measures showed significantly different patterns of LTP decay between groups. For the SLEEP animals, there was a gradual decay of LTP following its induction but the values remained significantly above BL levels 48 h after tetanization (10.2 ± 2.9%, $P < 0.05$). In contrast, the REMD and TSD animals exhibited a faster decay in LTP as revealed by fEPSP slope values returning to BL levels within 24 h and remaining stable at this level at the 48-h interval (1.2 ± 3.4% REMD, 5.0 ± 4.0% TSD). It should be noted that, at 5 h, LTP was at the same level as during the first 1 h after induction in the REMD and TSD animals (REMD: 0 h, 21.8 ± 5.3% vs. 5 h, 17.1 ± 3.9%, $P > 0.05$; TSD: 0 h, 16.4 ± 4.0% vs. 5 h, 20.2 ± 5.7%, $P > 0.05$), although significant decay was observed in the SLEEP animals (0 h, 24.0 ± 2.9% vs. 5 h, 17.9 ± 2.0%, $P < 0.05$).

For the population spike, no significant differences were observed in the maintenance of late-phase LTP among all groups (Fig. 4B). After LTP induction, the evoked responses decayed gradually following either sleep or sleep deprivation, but still remained potentiated (i.e. above BL levels) at 48 h in all groups (SLEEP, 160.2 ± 29.5%, $F_{4,44} = 31.8$; REMD, 133.3 ± 28.6%, $F_{4,32} = 19.2$; TSD, 96.6 ± 35.7%, $F_{4,16} = 11.2$; BL vs. 48 h, $P < 0.05$). At the short-term interval (5 h), LTP was maintained at levels similar to

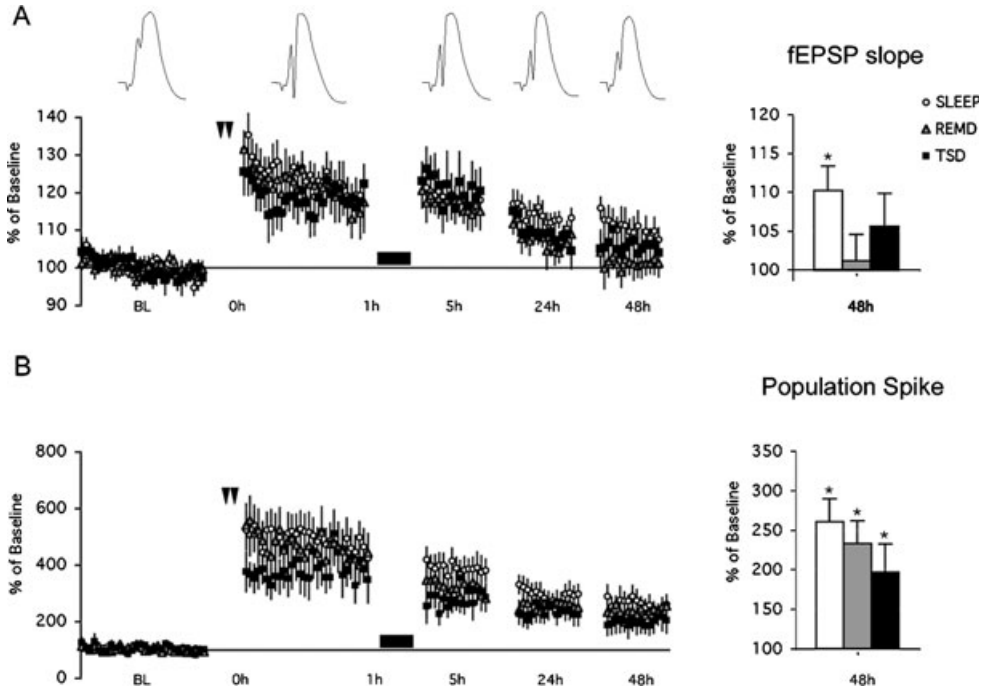

FIG. 4. Effects of sleep deprivation on LTP maintenance in the DG. Following HFS (arrows; 10 trains of 20 pulses at 400 Hz, every 10 s), no differences were observed in the levels of LTP induction (0 h) between the groups, as measured by both (A) fEPSP slope and (B) population spike. (A) Shortly after sleep deprivation (5 h), REMD and TSD fEPSP slopes did not differ from those immediately after tetanization. In contrast, animals allowed to sleep (SLEEP) had a slight but significant decay of their fEPSP slope. At 48 h, however, LTP returned to BL levels in the REMD and TSD animals, whereas SLEEP animals had their evoked responses still potentiated. (B) For the population spike no differences were observed in the long-term decay of LTP. However, at 5 h LTP values of SLEEP and REMD animals showed a significant decay whereas they remained potentiated in TSD animals. The black bar represents 4 h of sleep or sleep deprivation. LTP recordings at 5, 24 and 48 h were taken for 15 min (every 20 s) from each brain hemisphere. One-way ANOVA, repeated-measures, Newman–Keuls *post hoc* test. *$P < 0.05$, BL vs. 48 h. SLEEP group ($n = 12$), REMD group ($n = 7$) and TSD group ($n = 6$).

those observed immediately after tetanization in the TSD group ($P > 0.05$), whereas it decayed for the SLEEP and REMD groups ($P < 0.05$).

Figure 5 presents the time course of the population spike and fEPSP slope measured in the DG contralateral to the tetanized hemisphere. The contralateral hemisphere did not show potentiation of the

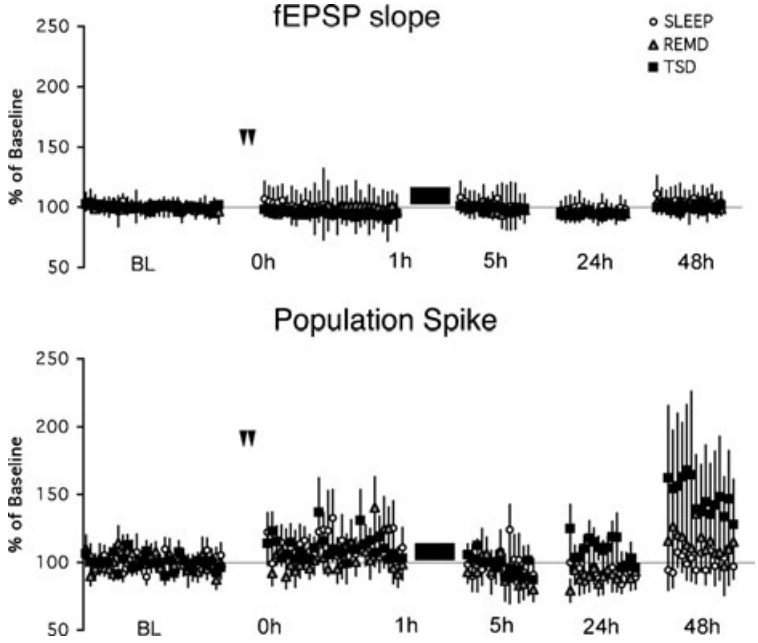

FIG. 5. Evoked responses recorded in the contralateral hemisphere of animals subjected to LTP in the DG. (A) Induction of LTP in the ipsilateral hemisphere (arrows) did not affect the potentials recorded from the contralateral DG. They also did not differ significantly from BL levels throughout the experiment. The black bar represents 4 h of sleep or sleep deprivation. LTP recordings at 5, 24 and 48 h were taken for 15 min (every 20 s) from each brain hemisphere.

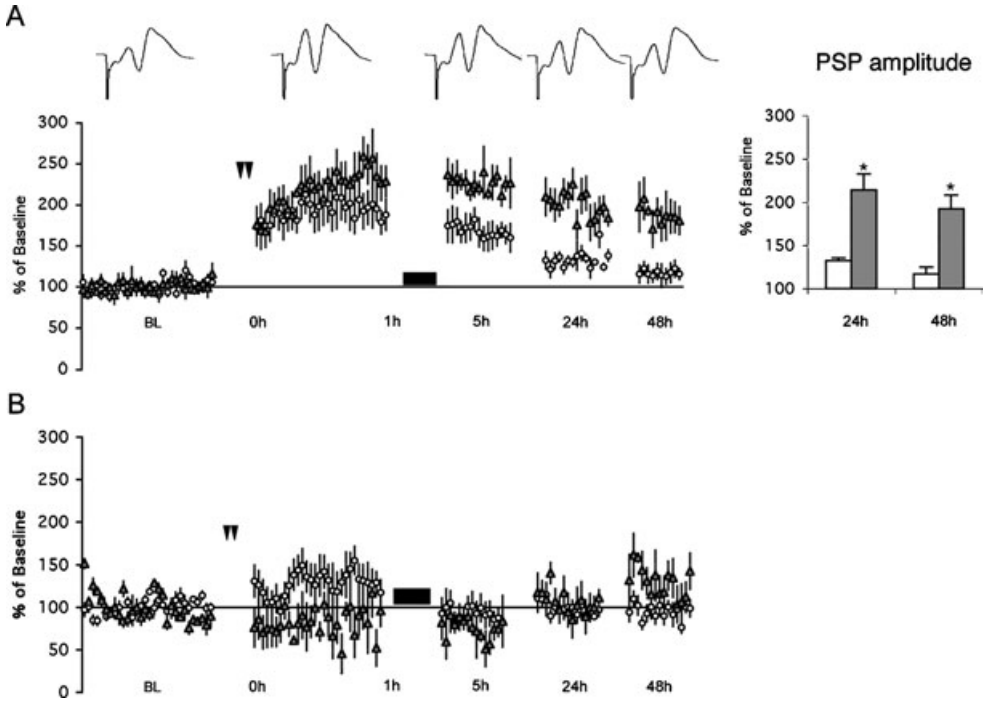

FIG. 6. Effects of REMD on the maintenance of LTP in the mPFC. Following HFS (arrows; two series of ten 50-ms trains at 250 Hz every 10 s, 10 min apart), no differences were observed in the levels of LTP induction (0 h) between the REMD and SLEEP groups. (A) Shortly after REMD (5 h), PSP amplitude levels did not differ from those immediately after tetanization (0 h). However, at 48 h the LTP values in SLEEP animals returned to BL levels whereas in the REMD animals they were still potentiated. (B) Ipsilateral induction of LTP in the mPFC did not affect the potentials in the contralateral hemisphere. The contralateral potentials were stable during the entire experiment. It should be noted that the data from animals with drifting potentials were discarded. The black bar represents 4 h of sleep or sleep deprivation. LTP recordings at 5, 24 and 48 h were taken for 15 min (every 20 s) from each brain hemisphere. One-way ANOVA, repeated-measures, Newman–Keuls *post hoc* test. *$P < 0.05$, BL vs. 48 h. SLEEP group ($n = 5$), REMD group ($n = 5$).

TABLE 1. Plasma CORT after 4 h of sleep or sleep deprivation

Group	[CORT] (ng/mL)	*n*
SLEEP	186.5 ± 18.1	9
REMD	144.7 ± 15.6	4
TSD	228.2 ± 9.1*	7

Data are shown as mean ± SEM. CORT, corticosterone; REMD, rapid-eye-movement sleep deprivation; TSD, total sleep deprivation. *$P < 0.05$ vs. REMD. *n*, number of animals in each group.

population spike or fEPSP slope after tetanization. In addition, the potentials were stable throughout the time course of the experiment (BL, 0 h, 5 h, 24 h, 48 h), with no significant differences between BL and any of the post-tetanization values (Population spike: SLEEP, $F_{4,28} = 2.35$; REMD, $F_{4,16} = 1.24$; TSD, $F_{4,20} = 1.88$, $P > 0.05$; fEPSP slope: SLEEP, $F_{4,36} = 0.66$; REMD, $F_{4,24} = 2.73$; TSD, $F_{4,24} = 0.89$, $P > 0.05$).

Medial prefrontal cortex

As shown in Fig. 6A, there was no difference in the LTP levels induced in the PSP amplitude of SLEEP and REMD animals (SLEEP, 91.2 ± 20.2%; REMD, 127.1 ± 17.3%; $t_8 = 1.35$, $P > 0.05$). At 5 h, LTP values were still similar to those immediately after tetanization for both groups: SLEEP (0 h, 92.2 ± 20.2% vs. 5 h, 67.6 ± 13.8%, $P > 0.05$) and REMD (0 h, 127.1 ± 17.3% vs. 5 h, 135.4 ± 14.2%, $P > 0.05$). SLEEP animals showed a trend towards reduced LTP, but this effect was not statistically significant. In contrast to the DG, however, 4 h REMD delayed the decay of the late-phase LTP in the mPFC. At 48 h, LTP was still above BL levels in REMD (92.2 ± 16.3%, $F_{4,16} = 33.9$, $P < 0.05$) compared to SLEEP (16.8 ± 8.1%, $F_{4,16} = 11.4$, $P > 0.05$) animals. Field potentials in the contralateral hemisphere were stable throughout the time course of the experiment (BL, 0 h, 5 h, 24 h, 48 h), with no significant differences between BL and post-tetanization values (SLEEP, $F_{4,12} = 1.48$; REMD, $F_{4,8} = 3.1$; all $P > 0.05$) (Fig. 6B).

Plasma corticosterone

To determine the level of stress in each treatment group, blood samples were collected from animals after 4 h of sleep or sleep deprivation. As shown in Table 1, the plasma CORT concentration in REMD and TSD animals did not differ significantly from SLEEP animals. TSD animals, however, had higher CORT levels than REMD animals. The estimated intra-assay variability was 8.9%.

Discussion

Our experiments revealed that REMD had opposite modulatory effects on hippocampal and mPFC synaptic plasticity. Four hours of REMD impaired late-phase LTP in the DG but prolonged the maintenance of late-phase LTP in the mPFC. In the DG, REMD did not affect neuronal excitability; there was no difference in the decay of the population spike LTP.

Sleep modulation of hippocampal LTP

Recent studies have reported that long-term sleep deprivation impairs synaptic plasticity in rat hippocampal slices (Campbell *et al*., 2002; Davis *et al*., 2003; McDermott *et al*., 2003). Particularly in the DG, 72 h of REMD impaired LTP 30 min after tetanization (McDermott *et al*., 2003). In our study, no changes were detected in LTP induction measured 1 h after tetanization. Differences between these studies, including REMD duration (4 h vs. 72 h), REM deprivation paradigm (handling vs. small platform), time of LTP induction (before or after REMD) and the brain preparation (freely behaving rats vs. slices), may account for this discrepancy. At longer times, we did observe that REMD impaired the late-phase (48 h) LTP.

Several studies have suggested that the physiological state of REM sleep provides favourable conditions for synaptic plasticity to occur. In the DG, both neuronal transmission and LTP are modulated by the animal's behavioural state (Winson & Abzug, 1977; Leonard *et al*., 1987; Bramham & Srebro, 1989; Bramham *et al*., 1994). Compared to awake and REM sleep, LTP induction is suppressed during SWS. Interestingly, LTP can be enhanced or suppressed depending on the phase of the hippocampal theta rhythm (Pavlides *et al*., 1988; Huerta & Lisman, 1993, 1995, 1996; Holscher *et al*., 1997; Hyman *et al*., 2003) which in rats occurs during exploratory behaviours and REM sleep. Possible information processing in sleep is also suggested from single-unit studies. It has been shown that hippocampal place cells that are active during a waking experience also have higher and more synchronized activity during subsequent SWS and REM sleep (Pavlides & Winson, 1989; Wilson & McNaughton, 1994; Louie & Wilson, 2001). It has further been shown that place cells fire in phase with the positive peak of the theta wave during ensuing REM sleep after rats are exposed to a novel environment but reverse their phase if exposed to a familiar one (Poe *et al*., 2000). During REM sleep, the activation of pontine–geniculo–occipital waves has also been shown to be involved in information processing (Mavanji & Datta, 2003; Datta *et al*., 2004). It is possible therefore that in our study 4 h REMD prevented the necessary level of neuronal activation for synaptic plasticity to be maintained in the long term.

Molecular studies have also reported that gene expression and protein synthesis during REM sleep are necessary for plasticity and learning and memory. In a number of early studies, it was reported that the post-training administration of the protein synthesis inhibitor anisomycin during REM sleep impaired learning (Fishbein & Gutwein, 1977; Gutwein & Fishbein, 1980; Smith *et al*., 1991). *Zif-268* is an activity-dependent immediate–early gene required for storage of long-term memories (Jones *et al*., 2001; Bozon *et al*., 2003; Lee *et al*., 2004). Recently, Ribeiro *et al*. (1999, 2002) reported that *zif-268* is specifically re-induced during REM sleep in several forebrain areas but remains at low levels during SWS sleep as compared to the awake state. Considering that *zif-268* is required for the expression of late-phase (24–48 h) LTP in the DG (Jones *et al*., 2001) and is down-regulated after short-term (3–6 h) sleep deprivation (Pompeiano *et al*., 1997), it seems possible that the reduction of *zif-268* after REMD is involved in the impairment of late-phase LTP observed in our study. This could affect genes regulated by *zif-268* which are involved in synaptic plasticity (Thiel *et al*., 1994; Berger *et al*., 1999). Additionally, the fact that sleep following the 4-h REMD period did not compensate for the maintenance of LTP suggests that there is a time window following tetanization when REM sleep is necessary for LTP consolidation.

Sleep modulation of prefrontal cortical LTP

In the mPFC, we observed that REMD had a positive modulatory effect on late-phase LTP. This observation is consistent with recent reports showing higher activation of the PFC following sleep deprivation in subjects previously trained in a verbal learning task

(Drummond *et al*., 2000; Chee & Choo, 2004). Drummond *et al*. (2000) also observed that the temporal lobe was not activated after sleep deprivation and that task performance was initially enhanced, but then declined. This is consistent with our results on the maintenance of hippocampal LTP where we found an enhancement of the early-phase LTP followed by an impairment of the late-phase LTP. A similar activation of the PFC in sleep-deprived subjects following a working memory task was also reported (Chee & Choo, 2004). It is also interesting to note that, in the cat visual cortex, REMD extends the developmental time window during which LTP can be induced (Shaffery *et al*., 2002).

In contrast to the hippocampus, *zif-268* expression increases in the frontal cortex following short-term (3–6 h) sleep deprivation (Pompeiano *et al*., 1997). This supports the idea of a double dissociation between the effects of REMD in the hippocampus and mPFC. In addition, protein synthesis in the mPFC is required for consolidation of fear extinction memories (Santini *et al*., 2004). The maintenance of late-phase LTP observed in the mPFC may also reflect changes in the cortical neurochemical milieu following REMD. It is known that the mPFC is densely innervated by dopaminergic and noradrenergic afferents from the ventral tegmental area and locus coeruleus (Levitt & Moore, 1978; Lindvall *et al*., 1978; Van Eden *et al*., 1987; Aoki *et al*., 1998). The increase in arousal state also alters dopamine levels in the PFC (Feenstra & Botterblom, 1996). In particular, REMD elevates dopamine concentration in the frontal cortex as well as the binding to its receptors (Nunes *et al*., 1994; Brock *et al*., 1995; Lara-Lemus *et al*., 1998). Dopamine also potentiates CA1–mPFC LTP (Gurden *et al*., 1999; Gurden *et al*., 2000; Otani *et al*., 2003) and modulates the maintenance but not the induction of mPFC LTP (Huang *et al*., 2004). Moreover, the sustained cholinergic and noradrenergic activity during REMD, as compared to sleep, could further contribute to enhancing LTP because both neurotransmitters are known to modulate cortical synaptic plasticity *in vivo* and *in vitro* (Brocher *et al*., 1992; Hasselmo & Barkai, 1995; Komatsu & Yoshimura, 2000). However, we cannot rule out the possibility that a different temporal window for disrupting LTP may exist, as demonstrated for spatial learning tasks (Smith, 1996). If that is the case, 4 h REMD at a different latency following tetanization could produce a similar impairment in the mPFC late-phase LTP as observed in the DG. This would suggest a temporal dissociation between mPFC and DG processes, during sleep, required for LTP maintenance.

Functional implications of sleep modulation of LTP

Although the mPFC and the hippocampus can interact during the execution of working memory tasks (Winocur, 1991; Gaffan *et al*., 1993; Morgan *et al*., 1993; Laroche *et al*., 2000), they have distinct and complementary roles (Winocur, 1991). Because LTP is considered a cellular correlate of memory storage, the most parsimonious interpretation of our findings would be that REM sleep enhances episodic memories in the hippocampus while erasing working memories in the prefrontal cortex. This is suggested by the relatively long-lasting deactivation of the dorsolateral frontal cortex observed during sleep in humans and a higher relative activation after REMD, associated with decreased temporal activity and performance deficits after REMD (Drummond *et al*., 2000; Chee & Choo, 2004). In addition, 4 h REMD immediately following training in the eight-arm maze impairs reference memory but has no effects on working memory (Smith *et al*., 1998). As an alternative explanation, the enhancement of late-phase LTP in the mPFC observed in our study could reflect a compensatory response to the arousal demands of REMD. Emotional memories involving circuits in the hippocampus, amygdala and mPFC could benefit from such synaptic enhancements after sustained arousal (Kilpatrick & Cahill, 2003). These effects could be mediated by a combination of specific changes in neuronal firing activity, gene expression and neurochemical modulation following REMD. In contrast to an exclusive role of REM sleep on maintenance of synaptic plasticity, it is also possible that the repetitive alternation between SWS and REM sleep is the important event disrupted during REMD and required for memory consolidation (Datta, 2000). In addition, Ribeiro *et al*. (2004) demonstrated that the correlated unit activity in cortex, hippocampus and thalamus in SWS occurred only in animals exposed to novelty. Upon the transition from SWS to REM sleep, the coexistence of cortical spindles and hippocampal theta oscillations could also provide a moment for cross communication between the cortex and hippocampus (Gottesmann, 1996; Mandile *et al*., 1996; Siapas & Wilson, 1998).

It is possible that the enhancement of LTP by REMD in the mPFC does not represent an improvement of memory consolidation. In the mPFC, REM sleep may serve to reset synaptic strength and restore synaptic plasticity for the following awake state. It is also conceivable that LTD, rather than LTP, subserves memory processes in the mPFC. Burette *et al*. (2000) showed that, in the hippocampo–mPFC pathway, enhanced working memory performance was correlated with LTD. Recent observations in our laboratory also demonstrate that induction of LTP in the hippocampus is associated with LTD in the mPFC. On the other hand, Herry & Garcia (2002) showed that, in the thalamus-mPFC pathway, LTP but not LTD was associated with the extinction of fear-conditioned memory. The functional correlates of LTP and LTD in the prefrontal cortex and the role that sleep may play are still unclear and need further investigation.

Conclusions

Sleep is a highly conserved physiological state in mammals. One possible function of sleep is the maintenance of synaptic plasticity subserving learning and memory. In the present study, we showed that REM sleep deprivation has opposite modulatory effects on LTP maintenance in the hippocampus and mPFC. REMD shortly after LTP induction impaired late-phase LTP in the hippocampus whereas it prolonged late-phase LTP in the mPFC. These results suggest that distinct memory processing takes place in these two brain areas during sleep.

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Abbreviations

AW, awake; BL, baseline; CORT, corticosterone; DG, dentate gyrus; fEPSP, field excitatory postsynaptic potential; HFS, high frequency stimulation ; IS, intermediate stage sleep; LTD, long-term depression; LTP, long-term potentiation; mPFC, medial prefrontal cortex; MPP, medial perforant pathway; PSP, postsynaptic potential; REM, rapid-eye-movement; REMD, rapid-eye-movement sleep deprivation; SWS, slow-wave sleep; TSD, total sleep deprivation.

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