Stress-Related Modulation of Hippocampal Long-Term Potentiation in Rats: Involvement of Adrenal Steroid Receptors

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Stress is usually known to modulate hippocampal long-term potentiation (LTP) as well as learning and memory (Kim and Diamond, 2002) and is usually evoked when animals are introduced into an apparatus used for testing spatial cognition (Morris, 1984; Kant et al., 1988; Sandi et al., 1997; Akriv et al., 2001). A bimodal effect of stress on learning and memory has been proposed (Diamond et al., 1992; Cahill and McGaugh, 1998; McGaugh, 2000; McGaugh and Roozendaal, 2002). At the cellular level, elevated stress impairs LTP in the CA1 and dentate gyrus (DG) regions of the hippocampus, both in vivo (Filipini et al., 1991; Pavlides et al., 1993; Xu et al., 1997; Pavlides et al., 2002) and in vitro (Foy et al., 1987; Shors et al., 1989; Kim et al., 1996; Zhou et al., 2000). Stress is correlated by increased release of corticosterone from the adrenal glands. Central actions of corticosterone are mediated by two corticosterone-binding receptors: the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR), the latter showing a 10-fold higher affinity for corticosterone than the former (De Kloet et al., 1993; van Steensel et al., 1996). Both receptor types are found in the hippocampus, which is also the brain region with the highest level of glucocorticoid receptor binding (McEwen et al., 1968; Reul and De Kloet, 1985; Reul et al., 1989). Whereas activation of GRs impairs hippocampal LTP, activation of MRs results in the facilitation of LTP (Pavlides et al., 1995; Kim and Yoon, 1998; Smigra et al., 1998; Pavlides and McEwen, 1999). Both receptor complexes regulate the expression of a variety of genes by directly binding to the DNA or via protein–protein interactions with other transcription factors (Diamond et al., 1990; Zhang et al., 1991; Cato et al., 1992a,b; Drouin et al., 1992, Herman, 1993; Malkoski et al., 1997).

Long-term potentiation can be divided into two major phases: protein synthesis-independent early LTP (3–4 hr) and protein synthesis-dependent late LTP with a duration of at least up to 8 hr (Krug et al., 1984; Frey et al., 1988, 2001; Matthies et al., 1990). The combination of a weakly stimulated input (eliciting early LTP) with a strong tetanization (inducing late LTP) of a second independent input within a time window of 30 min results in a prolongation of early LTP into late LTP in the first input, which is protein synthesis dependent (Frey and Morris, 1997, 1998). This late-associative interplay between two separate synaptic inputs has been explained by processes of “synaptic tagging” (Frey and Morris, 1997): the formation of a transient synaptic tag at a weakly stimulated input that has the potential to capture and process plasticity proteins whose synthesis is induced by a strong input, consequently reinforcing early LTP into long-lasting late LTP.

The Journal of Neuroscience, August 13, 2003 • 23(19):7281–7287 • 7281

Behavioral/Systems/Cognitive

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Similar behavioral reinforcements of an electrically induced...
early LTP in vivo by appetitive or aversive emotional stimuli were found under mild stress conditions (Izquierdo and Medina, 1995; Seidenbecher et al., 1997), depending on protein synthesis and on β-adrenergic activation. Akirav and Richter-Levin (2002) point out that a fast excitatory input from the basolateral amygdala (BLA) under high stress can serve as an “emotional tag,” resulting in an enhancement of DG-LTP.

This study aimed to examine stress effects on early DG-LTP within a vulnerable time window, with emphasis on the activation of corticosterone-binding and β-adrenergic receptors. Stress was elicited by behavioral manipulations (i.e., handling and swimming), which are related to spatial training paradigms.

Materials and Methods
Electrode and cannula implantation
Male Wistar rats (8 weeks of age) were anesthetized with Nembutal (40 mg/kg, i.p.). A monopolar recording electrode was implanted stereotaxically into the granule cell layer of the dentate gyrus [coordinates: antero-posterior (AP), −2.8; lateral (L), 1.8 from bregma, 3.2–3.5 ventral from dura] and a bipolar stimulation electrode was implanted into the perforant path (coordinates: AP, −6.9; L, 4.1, 2.2–2.5 ventral from dura) of the right hemisphere; coordinates are based on the atlas of Paxinos and Watson (1998). Each electrode consisted of an insulated stainless-steel wire 125 μm in diameter. During preparation, test pulses were delivered to optimize the population-spike amplitude (PSA). The animals were allowed at least 1 week to recover from surgery. For the pharmacological experiments, a cannula (coordinates: AP, −0.8; L, 1.6 from bregma) was additionally implanted into the right lateral ventricle.

Electrophysiological recording
Rats were placed into a recording box (40 × 40 × 40 cm), and the electrodes were connected to a swivel by a flexible cable. This allowed the freely moving animals ad libitum access to food and water. The responses were amplified (differential amplifier, Inh; Science Products, Hochheim, Germany), transformed by an analog-to-digital interface (CED 1401+; Cambridge Electronic Design, Cambridge, UK), and stored on a personal computer. Biphasic constant current pulses (0.1 mSec per half wave) were applied to the perforant path to evoke DG field potentials of the maximum PSA. Because the spike is required to induce LTP, the preparation was optimized to obtain a population spike. This influences the dipole of the field EPSP in the hilus, making the recording of the PSA more preferable than that of the EPSP. After registering a stable baseline for 1 hr, LTP was induced by weak tetanic bursts (three bursts of 15 pulses of 200 Hz with 0.2 mSec duration of each stimulus and 10 sec interburst interval; same stimulus intensity as for PSA testing). Two minutes and then every 15 min after tetanization, five test stimuli (10 sec interpulse interval) were delivered and the mean values of field potentials were stored for 8 hr. A 24 hr value was obtained the next day. For analysis and presentation, the 15 min recordings were averaged in groups of four to yield 1 hr values. The 2 min value served as control to determine whether a sufficient initial potentiation (with no more than 25% difference between individual animals) had been obtained.

Tetanization and experimental manipulations were always performed between 10:00 and 11:00 A.M. to avoid interferences with the diurnal rhythm of corticosterone titters.

Stress procedures and experimental groups
The swim stress apparatus was a circular plastic water tank 1.82 m in diameter and 58 cm in height filled with water up to a level of 38 cm. The water temperature was 25 ± 2°C. Water was made opaque by a white latex fluid (Sakret, Giessen, Germany). For behavioral manipulations, all animals were used only once.

Control group. Animals in this group received a weak tetanus and were then left undisturbed in the recording chamber.

Swimming group. Rats in the swimming group were placed in the maze 15 min after tetanus for a 2 min swim. They were then dried with a towel and transferred back into the recording chamber. Before swimming, the electrodes were protected from water immersion by petroleum jelly.

Handling group. The handling group was identical to the swimming group in every respect, except that animals were not transferred into the water tank.

Hormone analysis
Blood samples of all groups were collected at the same time of day after decapitation of the animals. Blood samples were taken from parallel groups of animals that had not been implanted with electrodes. However, the experimental and handling procedures were exactly the same as for the implanted animals, with the exception of the absence of recording or LTP induction. Rats were killed 15 min after either swimming or handling. Trunk blood was sampled within 25–30 sec from opening the cache and handling the animal. Blood was allowed to coagulate on ice in an adrenalin-coated tube. Then the blood was centrifuged, and the serum was stored at −20°C. Samples were analyzed by radioimmunoassay (RIA) within 4–8 weeks. RIA was performed as described previously (Stefanski et al., 2001).

Pharmacology
Glucocorticoid receptors were blocked by mifepristone, and mineralocorticoid receptors were blocked by spironolactone (150 ng, i.c.v. each; Sigma, St. Louis, MO). Both substances were dissolved in ethanol and then brought up to 1 ml volume with 0.9% saline with a final concentration of 50 ng/μl (2% ethanol). The control solution consisted of 0.9% saline (2% ethanol). The solutions were injected at 1 μl/min to a total volume of 3 μl via a Hamilton syringe. Propranolol (Sigma), a β-adrenergic receptor antagonist, was liquefied in 0.9% saline at 2 μg in a volume of 5 μl, which was applied over a period of 5 min. Injectors were placed into the cannula 30 min before tetanus, and the solutions were injected 1 min after tetanus. The injectors were left in place until the behavioral manipulations were performed.

Anisomycin (Sigma), a reversible protein synthesis inhibitor, was first dissolved in 15 μl of 1N HCl solution and then treated with 1N NaOH to create a pH of 7.0. The solution was subsequently made up to a 50 μl volume with 0.9% sodium chloride. After recording of the baseline, the substance (240 μg, i.c.v.; 5 μl over a 5 min period) or the vehicle was applied. After 1 hr, the animals received the weak tetanus.

Statistics
For group comparisons of overall differences in LTP between groups, the general linear model for repeated measures was chosen (slight differences in the degrees of freedom result from a few missing values). Least significant difference multiple-comparison (LSD) post hoc tests were used for multiple group comparisons. Differences in hormone levels were evaluated by the Mann–Whitney U test after an overall comparison with the Kruskal–Wallis H test. The 24 hr values for the drug-treated and vehicle-treated groups were compared by one-way ANOVA and LSD post hoc tests. All tests were two-tailed, and the level of significance was set at p ≤ 0.05.

Results
Swimming and handling modulated DG-LTP in opposite directions
A 2 min swim subsequent to handling resulted in prolonged LTP, up to 24 hr when compared with control animals (F(1,12) = 7.95; p = 0.014). Handling alone, in contrast, reversed early LTP and led to a suppression of PSA amplitudes below baseline (F(1,12) = 9.07; p = 0.01) (Fig. 1A). This bidirectional modulation of LTP became most obvious when swimming animals were compared with handled animals (F(1,12) = 21.77; p = 0.001). An overall difference, justifying the separate analyses, could be found between all three groups (F(2,19) = 13.97; p < 0.0001). Handling had no effect on baseline values, as indicated by a baseline control group (F(1,12) = 0.20; p > 0.1), whereas swimming slightly depressed baseline values (F(1,10) = 7.71; p < 0.05) (Fig. 1B). No
difference could be found between the baseline values for the swimming and the handling group ($F_{(1,10)} = 4.59; p > 0.05$).

**Blockade of GRs but not of MRs prevented impairment of LTP by handling**

We measured the titers of serum corticosterone in animals 15 min after the different behavioral manipulations and found significant overall differences ($\chi^2 = 18.59$; df = 2; $p < 0.001$). Group comparisons (Fig. 2) revealed that handling caused an increase in corticosterone that was threefold that seen for the control group ($U = 0; p < 0.01$), whereas swimming augmented the titers nearly sixfold, also with respect to the control group ($U = 0; p < 0.01$). Handled animals showed significantly lower corticosterone titers than swimming animals ($U = 0; p < 0.01$). This suggests an impact of corticosterone on the maintenance of LTP, depending on the animals’ manipulation.

The pharmacological analysis of the handling group alone revealed an overall difference between groups treated with a GR-antagonist (GR-ant), an MR-antagonist (MR-ant), or the vehicle ($F_{(2,13)} = 11.75; p = 0.001$). Application of a GR-ant prevented impairment of LTP compared with vehicle-treated (Fig. 3A) animals ($F_{(1,8)} = 18.60; p < 0.01$) and led to normal early LTP that was not distinguishable from that in the control group ($F_{(1,1,12)} = 2.71; p > 0.1$). Injection of an MR-ant, however, had no effect on the impairment of LTP when compared with vehicle controls (Fig. 3B).

**Inactivation of MRs but not GRs hindered LTP prolongation by swimming**

An overall comparison between all drug- and vehicle-treated swim groups (including the anisomycin- and propranolol-treated groups) revealed a significant difference ($F_{(5,36)} = 15.12; p < 0.0001$). Application of the GR-ant in animals that experienced a 2 min swim had no influence on LTP prolongation (Fig. 3C), whereas an acute blockade of MR receptors completely impaired LTP in swimming rats ($F_{(1,9)} = 43.76; p < 0.001$), with a significant difference at all time points (Fig. 3D) from the second hour onward. It is known that acute blockade of MRs results in an increased release of corticosterone. This could lead to an overactivation of GRs that would then mask the effect of MR blockade on LTP. For this reason, a group treated with a mixture of the GR-ant and MR-ant was tested. We found no difference between the MR-ant and the GR-ant–MR-ant group (Fig. 3E), but a difference was found between vehicle-treated rats and the GR-ant–MR-ant group ($F_{(1,9)} = 20.18; p < 0.01$) that was similar to that ascertained between the vehicle-treated rats and the MR-ant group. Mifepristone ($F_{(1,10)} = 1.36; p > 0.1$) as well as spironolactone ($F_{(1,10)} = 0.25; p > 0.1$) did not operate on baseline values, as reflected by the lack of effect on a baseline control group (Fig. 3F).

The blockade of GRs had no significant effect compared with vehicle controls but displayed a slight enhancement of LTP up to 6 hr. In contrast, the blockade of MRs led to a suppression of early LTP similar to that in handled animals. The MR-ant-treated swimming group exhibited a significantly lower potentiation than control animals ($F_{(1,12)} = 20.07; p < 0.01$) with significant differences from the second hour onward up to 7 hr ($p < 0.01$ each; $p < 0.05$ for the 6 and 7 hr time points).

**Reinforcement of LTP was dependent on protein synthesis but not on β-adrenergic activation**

The stress response to swimming leads not only to an increased level of blood corticosterone but also to a release of adrenaline.
and noradrenaline. These substances do not readily cross the blood–brain barrier. The main source of noradrenaline in the brain is the locus ceruleus, and there are several lines of evidence that the activation of $\beta$-adrenergic receptors plays a role in the prolongation of early LTP by behavioral reinforcement. Therefore, we tested the influence of $\beta$-adrenergic activation with a group of animals treated with propranolol, an unspecific $\beta$-adrenergic antagonist (Fig. 4 A). We could not state significant differences between this group and the vehicle-treated group.

To determine whether the late phase of the LTP reinforced by swimming is protein synthesis dependent, anisomycin, a protein synthesis inhibitor, was applied before behavioral manipulation. Anisomycin prevented the prolongation of early LTP by swimming (Fig. 4 B), indicated by a significant difference with the vehicle-treated rats ($F_{(1,10)} = 10.09; p = 0.01$). Figure 5 gives an overview of the differences at the 24 hr time point between treated rats in the swimming groups. In previous studies from our laboratory, it was shown that propranolol (Seidenbecher et al., 1997) and anisomycin (Frey et al., 2001) at the same doses and under the same protocol used in this study did not affect baseline values; therefore, no baseline control experiments have been conducted for these substances.

**Discussion**

We found bidirectional effects of behavioral manipulations on the maintenance of hippocampal LTP. Although handling 15 min after induction of early LTP resulted in an impairment of LTP, a 2 min swim, also 15 min after induction, resulted in prolongation of LTP to up to 24 hr. Because both of the behavioral manipulations increased the titers of circulating corticosterone, we studied the role of corticosterone receptors on LTP modulation by behavioral manipulation. The handling-dependent LTP impairment was reversed by blockade of glucocorticoid receptors and left unaffected by blockade of mineralocorticoid receptors. The LTP prolongation observed after swimming, however, was unaffected by blockade of GRs, whereas blockade of MRs resulted in an impairment of LTP comparable with that seen in untreated handled animals.

A possible explanation for the pattern of results obtained can be found in the finding by Gesing et al. (2001) that swim stress leads to a significant upregulation, within 24 hr, of MRs in the hippocampus (cf. Reul et al., 2000). Under basal conditions, as a result of their differential binding capacity, all MRs but not GRs will be occupied. After swimming, both the upregulation of MRs and the increased levels of corticosterone would result in a shift in the balance of MR–GR occupation, so that MR-induced modulatory effects on LTP would then overcome those of the GRs. The failure to observe an MR-antagonist effect in handled animals suggests no change in corticosterone-binding receptors. Accordingly, the activation of GRs may exceed that of MRs and lead to the impairment in LTP observed, which can be reversed by inhibition of the GRs but is left unaffected by inhibition of the MRs. This is supported by the finding that blockade of the MRs before swimming also impairs LTP, comparable with that of animals that were only handled. Therefore, the MR effect triggered by the swimming experience may overcompensate the GR effect and leads not only to a reversal but also to prolongation of LTP. Such a mechanism may at least function during acute high stress and acute MR inhibition. During chronic stress and subchronic sys-
Systemic injection of spironolactone, Herman and Spencer (1998) identified increased levels of GR mRNA in CA1 and DG similar to that observed in adrenalectomized rats. They concluded that activation of MRs tonically inhibits GR biosynthesis in the hippocampus. A diminution or an increase in MR- over GR-mediated neuronal effects may regulate the neuronal responsiveness during stressful situations and may adjust behavioral adaptation (De Kloet et al., 1993; Joels and De Kloet, 1994). However, De Kloet et al. (1999) pointed out that the impairment of LTP and the facilitation of long-term depression (LTD) during stress does not merely depend on the occupation of corticosteroid receptors but on the history of activation of different inputs during previous events (e.g., activation of transcription factors), so that even during mild stress unrelated to a learning paradigm, the synaptic strength can be decreased. Such mechanisms may play a role in the reversal of LTP observed in our handled group, where the animals had experienced handling during the daily keeping routine.

The activated corticosterone receptors regulate gene expression in two ways: by transactivation, which requires homodimerization and binding of homodimers to the DNA, and through transrepression, by interaction of receptor monomers with other transcription factors, which does not require DNA binding (Heck et al., 1994). For CA1 pyramidal neurons, DNA binding is required to activate voltage-gated calcium channels by corticosterone (Karst et al., 2000). Our finding, that the LTP reinforcement is protein synthesis dependent, suggests that the protein products mediated by the MR activation play a role in the transformation processes of synapses related to late LTP in DG-granule neurons. In previous studies on the CA1 region of the hippocampus (Xu et al., 1997), it has been found that behavioral stress (exposure to an elevated platform) facilitates the induction of LTD and blocks the induction of LTP in anesthetized rats. This effect could be reversed by application of a GR-antagonist as well as a protein synthesis inhibitor before stress (Xu et al., 1998a).

Overall, these results suggest a role of GRs in the control of long-lasting CA1 synaptic plasticity, because a strong tetanization protocol was used in this study to induce a protein synthesis-dependent LTP. The pattern observed in our handled group, where reversal of early LTP, which is protein synthesis independent, can be blocked by a GR-antagonist, suggests that the activation of GRs is also involved in cellular processes not related to gene expression in the DG. Rapid actions of GRs on cellular signaling pathways, such as activation of MAP kinase (mitogen-activated protein kinase), adenyl cyclase, or protein kinase C (Cato et al., 2002), and other effects increasing the intracellular Ca²⁺ levels (Kerr et al., 1992; Kim and Yoon, 1998; Bhargava et al., 2000) have been described previously.

The prolongation of LTP by swimming does not depend on the activation of β-adrenergic receptors. Interestingly, the latter is reported for behavioral reinforcement experiments. Seidenbecher et al. (1997) pointed out that appetitive stimuli, such as water delivery to water-deprived rats, aversive stimuli, such as footshocks, or voluntary spatial exploration of a novel environment (Straube et al., 2003), when given around a weak tetanus, resulted in a β-adrenergic-dependent prolongation of DG-LTP. A β-adrenergic-dependent reinforcement of DG-early LTP can also be elicited by electrical stimulation of the BLA, a structure that is seen to be involved in the processing of emotionally arousing information (Akirav and Richter-Levin, 1999, 2002; Frey et al., 2001). In contrast, evidence for a CA1-LTP impairing effect of the amygdala has been raised (Kim et al., 2001).

The main difference between these reports and our experiments is the highly stressful context in which our study was conducted. Increased extracellular levels of corticosterone within the hippocampus could already be observed a few minutes after the onset of stress (Linthorst et al., 2000) and may interfere with the β-adrenergic processes induced by arousing novelty. Some mechanisms of an inter-

Figure 4. Population spike (PS) amplitudes (percentage change from baseline values) over 8 hr and a 24 hr value for rats that experienced a 2 min swim after tetanus and were injected with a β-adrenergic antagonist (A) or a protein-synthesis inhibitor (B) (p = 0.004, 0.03, 0.0001, levels for increasing time points). Means ± SEM are given. Asterisks indicate significant time point differences. Dashed lines indicate the 100% level.

Figure 5. Differences between the population spike amplitudes at the 24 hr time point for the drug-treated swimming groups. Vehicle post, injection after tetanization; vehicle pre, injection before tetanization, control for the anisomycin-treated group. Means ± SEM are given. **p < 0.01; *p < 0.05.
play between β-adrenergic receptor activation and glucocorticoid receptors have been reported for different brain regions (Duman et al., 1989; Schmidt et al., 2001; Roozenendaal et al., 2002) with little evidence of mutual impairment in the dentate gyrus. Smigra et al. (1998) found in dentate granule cells of adrenalectomized but not intact rats that the LTP-enhancing effect of MR activation depends on β-adrenergic activity.

Because we found no evidence for the requirement of β-adrenergic activation for DG-LTP reinforcement in our study, an interplay between corticosterone-binding receptors and other types of receptors or transmission systems is very likely and remains to be investigated. This could involve the serotonergic (Shakesby et al., 2002) or the cholinergic system, which has been implicated in DG-LTP reinforcement (Frey et al., 2001). An involvement of the septohippocampal cholinergic system in an adaptive response to stress has been reported (Gilad, 1987). This includes a direct activation of hippocampal cholinergic terminals by corticosterone within minutes after a stressful event, with increased release of newly synthesized acetylcholine (Gilad, 1987; Gilad et al., 1987). In addition, a modulatory effect of the BLA on DG-LTP via cholinergic medial septum pathways seems likely (Spanis et al., 1999; Frey et al., 2001).

The novelty of the swim situation very likely contributes to our results. It has been found that perception of a novel environment under low-stress conditions prolongs early DG-LTP within a certain time window around a weak tetanus (Straube et al., 2003). A post-tetanus (2 min) exposure to 1 min of novelty prolongs early LTP, whereas a lasting novelty exposure impairs LTP. Similar results are found in the CA1: previously induced LTP by a strong tetanization protocol is reversed by lasting novelty exposure (Xu et al., 1998b), but the induction of CA1-LTP is facilitated in a dopamine-dependent manner by a brief (5 min) exposure (Li et al., 2003). Thus, the short-lasting swim experience in our study may also contribute to the facilitation of LTP. In addition, evidence has been raised that MRs are mediating behavioral reactivity during novel situations (Oitzl et al., 1994), whereas activation of GRs by stress during learning tasks is seen to facilitate the consolidation of information (Sandi et al., 1997; De Kloet et al., 1999; Shors, 2001). In comparing these studies, it is important to keep in mind that different mechanisms may underlie the effects of corticosteroid on the induction of LTP or on the modulation of an already induced LTP, as in our study.

It is well established that glucocorticoids modulate spatial learning (Oitzl and De Kloet, 1992; Sandi, 1998; Roozenendaal et al., 1999), and that genomic processes are involved (Oitzl et al., 2002). There is much evidence that GRs are involved in the consolidation of acquired spatial information in the water maze and the Y-maze, whereas MR modulates the behavioral reactivity to novel stimuli (Oitzl et al., 1992, 1993; Conrad et al., 1999; De Kloet et al., 1999). However, in other learning paradigms, pharmacological effects were less distinct. Douma et al. (1998) reported impaired reference memory in a hole board task after MR but not GR blockade, whereas working memory was impaired only after a combined inhibition of MRs and GRs. However, the combined analysis of glucocorticoid effects on hippocampal LTP and spatial learning and memory remains to be conducted.

References


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