Exposure to a novel environment interferes with the induction of hippocampal primed burst potentiation in the behaving rat

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Primed burst (PB) potentiation is a low threshold form of long-term potentiation that is induced by a pattern of electrical stimulation that mimics specific features of hippocampal physiology. In our paradigm, stimulation of the hippocampal commissural afferents composed of a single priming pulse, followed 170 msec later by a burst of four pulses at 200 Hz, induces PB potentiation of the CA1 population spike. We now report that the capacity for patterned stimulation to induce PB potentiation in behaving rats is affected by the animals' experience with the recording procedures. Specifically, PB potentiation occurred in only 15% of the first recording sessions. With continued stimulations over the course of days, the incidence of PB potentiation increased: Lasting effects occurred in 30% of the second, 75% of the third, and 92% of the fourth through sixth recording sessions. In additional studies, acclimation to the environment, rather than a kindling-like phenomenon, was identified as the critical precondition for PB potentiation to occur. Thus, our findings indicate that exposure of a rat to a novel environment results in a profound, but temporary, inhibition of hippocampal plasticity. The relationship of this work to studies of stress and hippocampal-dependent learning is discussed.

Long-term potentiation (LTP) is a long-lasting enhancement of synaptic efficacy that is induced by high-frequency electrical stimulation (Teyler & DiScenna, 1987). LTP has received much attention as a model of memory formation because it shares characteristics with memory, including rapid onset, long duration, and strengthening with repetition (Barnes, 1979; Teyler & DiScenna, 1984). In addition, pharmacological treatments that interfere with the induction of hippocampal LTP can also interfere with hippocampal-dependent learning (Morris, 1989; Morris, Anderson, Lynch, & Baudry, 1986). Thus, an enhanced understanding of LTP may lead to a greater understanding of the neurobiology of memory formation.

Historically, LTP has been induced by relatively long trains of high-frequency stimulation (e.g., 100 Hz for 1 sec). More recently, investigators have demonstrated

that the threshold for inducing LTP in the CA1 field and the dentate gyrus is substantially reduced when afferent stimulation is patterned to mimic frequencies of the hippocampal theta rhythm (Diamond, Dunwiddie, & Rose, 1988; Greenstein, Pavlides, & Winson, 1988; Larson, Wong, & Lynch, 1986; Rose & Dunwiddie, 1986; Staubli & Lynch, 1987). Specifically, Rose and Dunwiddie (1986) demonstrated that LTP could be induced by only 5 pulses: a single *priming* pulse, followed 170 msec later (i.e., at a theta frequency of 6 Hz) by a high-frequency *burst* of 4 pulses at 100 Hz. In contrast, a continuous train of as many as 10 pulses at 100 Hz was ineffective (Diamond, Dunwiddie, & Rose, 1988). The pattern-sensitive form of LTP has been termed *primed burst* (PB) potentiation (Rose & Dunwiddie, 1986). PB potentiation appears to be similar to LTP in most respects, such as the critical involvement of the NMDA receptors (Diamond, Dunwiddie, & Rose, 1988; Larson & Lynch, 1988), except that it is induced with far fewer stimulation pulses. (See Diamond, Dunwiddie, & Rose, 1988, for a more detailed comparison of LTP and PB potentiation).

The present study is an extension of our previous characterization of PB potentiation. We reported that, in the

This work was supported by the Veterans Administration Medical Research Service, NIDA Grant DA02702, and NSF Grant BNS 8811486 to G. M. Rose, and ADMH Postdoctoral Training Grant 2534281 to D. M. Diamond. Address correspondence to Greg M. Rose, Medical Research (151), VAMC, 1055 Clermont St., Denver, CO 80220.

behaving animal, PB potentiation occurred in only 65% of the stimulation attempts (Diamond, Dunwiddie, & Rose, 1988). In a more fine-grained analysis of the data, we have determined that PB potentiation rarely occurred during the first recording session. Moreover, the incidence of PB potentiation increased with each subsequent PB stimulation attempt. Consequently, most of the PB potentiation effects described in our earlier work occurred only after the animals had extensive experience with the recording procedures.

Exposing an animal to a novel environment is stressful (Davis et al., 1962; Hennessy & Levine, 1978; Pfister & King, 1976). Furthermore, hippocampal physiology (Dafny, Phillips, Taylor, & Gilman, 1973; Reiheld, Teyler, & Vardaris, 1984; Rey, Carlier, & Soumier-Mourat, 1987; Vidal, Jordan, & Zieglgänsberger, 1986) and plasticity (Bennett, Diamond, Fleshner, & Rose, 1989; Diamond, Bennett, Engstrom, Fleshner, & Rose, 1989; Dubrovsky, Liquornik, Noble, & Gijsbers, 1987; Gold, Delanoy, & Merrin, 1984) are affected by stress hormones. Therefore, one possible basis of our findings was that, when the animals were naive, the stress associated with exposure to an unfamiliar environment interfered with the induction of PB potentiation. Alternatively, the increased incidence of PB potentiation could have occurred independently of the animals' acclimation to the environment. Repeated ineffective PB stimulations may have decreased the threshold for inducing plasticity, in a manner analogous to kindling (Kairiss, Racine, & Smith, 1984; Sutula & Steward, 1986).

In the present paper, we have documented an increase in the incidence of PB potentiation following repeated stimulation sessions. We also sought to distinguish whether this increased incidence of PB potentiation over sessions resulted from the animals' acclimation to the environment or was a kindling-like phenomenon.

METHOD

Animal housing and surgical techniques were similar to those reported previously (Diamond, Dunwiddie, & Rose, 1988). Group-housed (2–3/cage) male Sprague-Dawley rats (270–350 g; Harlan Laboratories, Indianapolis, IN) were pretreated with atropine methyl nitrate (0.2-mg/kg, i.p.) and then anesthetized with secobarbital (50-mg/kg, i.p.). In some cases, implants were performed with the subjects anesthetized by Innovar-Vet (Pitman Moore) diluted to a 25% concentration with distilled water (1-ml/kg, i.p.). Supplementary doses of either secobarbital or Innovar-Vet were administered as necessary.

After surgical-level anesthesia was reached, the skull was cleared of connective tissue and holes were drilled for support screws, ground and stimulator indifferent wires, and a microdrive base. A microdrive (Deadwyler, Biela, Rose, West, & Lynch, 1979) was positioned over the recording site. A microelectrode (epoxylite-insulated tungsten, impedance 0.5–1.0 M Ω at 1 kHz) was lowered into the CA1 pyramidal cell layer, which was identified by complex spike activity occurring between 1.8–2.3 mm below the brain surface. The stimulating electrode (125 μ m diameter stainless steel Teflon-coated wire, uninsulated at the tip) was lowered into the left side of the ventral hippocampal commissure (coordinates AP –1.8, ML 1.0). The final stimulator depth ranged from 3.1–3.7 mm across

animals and was determined by optimizing the amplitude of the stimulus-evoked CA1 population spike (Anderson, Bliss, & Skrede, 1971). The microdrive and the microelectrode were removed at the end of the surgery. A cap was placed over the opening of the microdrive base. Dental cement was used to affix the wires, a plastic connector plug, and the microdrive base to the skull.

The standard experimental protocol was identical to that reported previously (Diamond, Dunwiddie, & Rose, 1988). On the day before testing (Day 0), a microdrive loaded with a recording electrode was attached to the base. On this day and all subsequent days of recording, the rats were handled extensively (20–40 min/day) prior to being placed in the recording chamber. The electrode was slowly lowered to the CA1 cell layer in approximately 1–3 h. After determining the location of CA1, the electrode was raised approximately 400 μ m to minimize tissue damage that might have occurred with small movements of the tip. All animals were given 5–7 h of exposure to the chamber on Day 0. The purpose of the Day 0 procedures was solely to locate the recording electrode proximal to the CA1 cell layer; PB stimulation was never given on Day 0.

At 0900 of the following day (Day 1), the recording electrode was again lowered into the CA1 cell layer. Final placement of the electrode occurred between 1000 and 1200 h. Baseline data were obtained when motor activity had ceased. Baseline stimulation (pulse duration 150 μ sec, 1–10-V range across sessions) began at 1400–1600 h in all cases. Stimuli were delivered at a rate of 1/30 sec, at an intensity that reliably evoked a population spike that was approximately 25% of the maximal response. All recording sessions were terminated between 1500 and 1700 h.

PB stimulation consisted of a single priming pulse followed 170 msec later by a burst of four pulses at 200 Hz. All stimulation pulses (test pulses and PB stimulation) were at the same voltage throughout a recording session. It is known that the amplitude of hippocampal evoked potentials (Winson & Abzug, 1977) and the development of LTP (Bramham & Srebro, 1989; Leonard, McNaughton, & Barnes, 1987) are affected by the behavioral state of the subject. To minimize state-dependent variables, PB stimulation was delivered in all cases while the animals were in a stable and reproducible behavioral state: the still alert behavioral state (SAL). SAL was reliably induced by opening the door to the acoustic chamber and delivering a brief sound, such as a hand clap. This procedure is similar to the induction of SAL by other investigators (e.g., Bramham & Srebro, 1989; Winson & Abzug, 1977). Previously, we demonstrated that the change in behavioral state to SAL in concert with a continuous train of five pulses did not result in long-term changes in the CA1 evoked response (Diamond, Dunwiddie, & Rose, 1988). A lasting enhancement of the evoked response was dependent on the delivery of PB stimulation.

When PB potentiation occurred (statistical analyses are described below), the microdrive was removed at the end of the recording session, and the rat was returned to the vivarium for 1–4 weeks. PB stimulations were given as many as six times per subject over the course of 3–6 months. If no change in response occurred on Day 1, the microelectrode remained in place, and the stimulation procedure described above was repeated 1–3 days later. PB stimulation was given once per session until a significant increase in the evoked response occurred or until a maximum of six patterned trains had been delivered. Recordings were not continued if there was a deterioration of the evoked response.

Two additional groups of rats were tested under a modification of the experimental protocol described previously. As in the standard protocol, the microdrive was attached to the base on Day 0 and all animals spent 5–7 h in the recording chamber. In one group ($n = 6$; multistimulation group), the animals were given three PB stimulations at hourly intervals (1200, 1300, 1400 h) on Day 1. At the end of Day 1, the microdrive was removed and the animals were not used any further. In a second group ($n = 8$; preacclimated group), the subjects were explicitly acclimated to the recording

procedures prior to the delivery of the first PB stimulation; these animals received extensive handling (30–60 min/day) and exposure to the recording chamber (5–7 h/day) for 7 days. The first PB stimulation train was delivered to preacclimated animals on Day 7.

A computer was used to digitize, automatically measure, and continuously display the population spike. Analysis of the amplitude of the population spike and statistical analyses were performed for each animal by comparing responses obtained during the 5-min period immediately prior to PB stimulation to those obtained during the 1–2-min (posttetanic potentiation [PTP] analysis) and 11–20-min periods (PB potentiation analysis) after PB stimulation. A *t* test was used for analysis of individual sessions, and a repeated measures multivariate analysis of variance (MANOVA) was used for group mean comparisons; the significance level was set at $p = .05$.

RESULTS

In a previous study, we reported that, in behaving rats, patterned stimulation was effective at inducing PB potentiation in 65% (17/26) of the attempts (Diamond, Dunwiddie, & Rose, 1988). Data from these previous 26 recordings plus an additional 33 recordings in the present study (for a total of 59 recording sessions in 29 animals) served as the current database.

The animals were given PB stimulation as many as six times over the course of 3–6 months of recordings. We analyzed the incidence and magnitude of PB potentiation as the animals progressed from being naive to well experienced with the stimulation/recording procedures. There was an increase in the incidence of PB potentiation with each subsequent recording session. PB potentiation occurred in only 15% (2/13) of the initial sessions, and it increased to 30% (3/10) in the second, 75% (6/8) in the third, and 92% (12/13) in the fourth through sixth sessions (Figure 1). The skewed distribution of the incidence of PB potentiation increasing in later sessions is significant [$\chi^2(3) = 19.1, p < .001$].

For recordings in which PB potentiation occurred, the mean magnitude of the PB potentiation did not differ

Figure 1. The incidence of primed burst (PB) potentiation increased with each subsequent recording session. The numbers in parentheses indicate the significant effects per total recordings. The sample sizes decrease after the first session, because technical limitations eliminated some animals from the study. There were 13, 10, 8, and 5 animals in the first, second, third, and fourth through sixth sessions, respectively.

Figure 2. The magnitude of primed burst (PB) potentiation was independent of the recording session. The data are expressed as the magnitude of PB potentiation in the individual recordings ($M \pm SE$). The sample size for each session is indicated in parentheses. Only sessions in which significant effects occurred were included in this analysis.

across sessions [$F(3,19) = 0.24, p = .87$]. These data are presented in Figure 2. There was also no difference in the magnitude of short-term plasticity (PTP) occurring 1–2 min posttetanus [$F(3,22) = 0.75, p = .53$; data not shown]. Because there appeared to be an increase in the magnitude of PB potentiation in the later recording sessions relative to that in the first recording session (Figure 2), we performed a post hoc analysis of the data. Comparison of the magnitude of PB potentiation in the first session ($n = 2$) versus the magnitude of PB potentiation in the second through sixth sessions ($n = 21$) revealed no statistically significant differences (PTP analysis, Mann-Whitney *U* test, $U = 9.0, p > .1$; PB potentiation analysis, $U = 7.0, p > .1$). It is possible that additional recordings may reveal a difference between the magnitude of PB potentiation in the early versus late recording sessions. However, owing to the extremely rare occurrence of significant PB potentiation effects in the initial recording session, this possibility is difficult to test. Overall, these analyses suggest that when PB potentiation occurred, the magnitude of the response was independent of the session number.

Two new groups of rats were used to evaluate the basis of the increase in the incidence of PB potentiation over sessions. One group of rats was given routine exposure to the recording procedures—that is, 2 h of handling and 14 h of exposure to the recording chamber on 2 contiguous days. On Day 1, PB stimulation was given once per hour for 3 h (multistimulation group). A second group of rats was preacclimated to the handling and recording procedures; the first PB stimulation train was given on Day 7 (preacclimated group).

Data from the multistimulation group indicated that three PB stimulations given to nonacclimated rats were ineffective. In no case (0/6 animals) was there a lasting change in the evoked response of animals in the multistimulation group [$F(3,30) = 0.37, p = .78$]. Data from

Figure 3. The basis of the increased incidence of primed burst (PB) potentiation with repeated sessions is acclimation. The top graph indicates that the first (filled triangles) and the third (open triangles) PB stimulations on Day 1 were ineffective ($n = 6$). Neither short-term nor long-term changes developed in these naive animals. The bottom graph illustrates the robust increase in response that developed in animals that were acclimated to the recording procedures prior to receiving their first PB stimulation (filled circles; $n = 8$). Data from all naive animals (open circles; $n = 13$) show no significant change in response. PB stimulation was given at Time 0. In both graphs, data are expressed as the mean $\pm SE$ for 1-min values.

the first versus the third PB stimulation on Day 1 are presented in Figure 3 (top). These data illustrate that there were no significant changes in the amplitude of the population spike in nonacclimated animals. By contrast, PB potentiation occurred in the majority (75%; 6/8) of the animals in the preacclimated group. The difference in the incidence of [2/13 vs. 6/8; $\chi^2(1) = 5.15$, $p = .02$] and overall magnitude [MANOVA, $F(3,54) = 8.18$, $p < .001$] of PB stimulation effects between control (first PB stimulation on Day 1) and preacclimated (first PB stimulation on Day 7) groups is significant. Tukey-Kramer a posteriori analysis revealed that the preacclimated group had a significantly greater response than the control group in both the PTP (1–2-min) and the PB potentiation (11–20-min) time periods ($p < .01$; see Table 1 and Figure 3, bottom).

Acclimation to the environment may have been accompanied by a change in the general excitability of the hippocampus. If this were the case, an increase in hippocampal excitability with acclimation may have facilitated the induction of PB potentiation in the later sessions. We evaluated this possibility by analyzing two measures of general excitability: baseline (pre-PB) stimulus current and baseline population spike amplitude. Both stimulus voltage and baseline evoked responses revealed no significant change with session number [ANOVA: stimulus voltage, $F(38,3) = 0.92$, $p > .1$; Tukey-Kramer: baseline evoked responses, $p > .1$; see Table 2]. Similarly, comparison of naive control animals (first PB stimulation on Day 1) with preacclimated subjects (first PB stimulation on Day 7) also revealed no difference in stimulation voltage levels or baseline population spike amplitudes

Table 1
Effects of Handling on Baseline Stimulation Voltage (V) and
Evoked Responses (mV)

	Stimulation (V)	Baseline (mV)	PTP (mV)	PB (mV)
Control Session 1	6.08 ± 1.14	1.10 ± 0.18	1.38 ± 0.22	1.13 ± 0.05
Handled Session 7	8.60 ± 1.77	1.12 ± 0.22	2.67 ± 0.48*	1.73 ± 0.35*

Note—PTP = posttetanic potentiation, PB = primed burst potentiation. Control $n = 13$, handled $n = 8$. * $p < .001$.

[ANOVA: stimulus voltage, $F(1,14) = 1.27$, $p > .1$; Tukey-Kramer: baseline evoked responses, $p > .1$; see Table 1). These data indicate that the increased incidence of PB potentiation in acclimated animals was not a function of a generalized change in hippocampal excitability.

DISCUSSION

The major finding in the present study is that the incidence of hippocampal PB potentiation is reduced when animals are exposed to a novel environment. PB potentiation rarely occurred during the animals' initial recording sessions. The incidence of PB potentiation increased with each subsequent recording session; by the fourth through sixth sessions, PB potentiation occurred after most attempts.

Basis of the Increased Incidence of Primed Burst Potentiation with Repeated Attempts

We considered two explanations for the increased likelihood of PB potentiation in later sessions. First, the initial presentations of apparently ineffective PB stimulation may have induced subthreshold cellular events that would enhance the likelihood that PB potentiation would occur in subsequent sessions. We refer to the first possibility as the *kindling* hypothesis, on the basis of its similarity to other work demonstrating that repeated subthreshold stimulation reduces the threshold for the induction of hippocampal plasticity (e.g., Kairiss et al., 1984; Sutula & Steward, 1986).

To test the kindling hypothesis, a group of nonacclimated rats were given PB stimulations repeatedly, at 1-h intervals. If subthreshold effects of PB stimulation summate until a plasticity threshold is reached, then there should have been an increased incidence of PB potentiation in the stimulations occurring with the second and third stimulation attempts. However, the data did not support the kindling hypothesis; multiple PB stimulations delivered to nonacclimated rats never induced PB stimulation. These findings provided evidence that ineffective PB stimula-

tion does not appear to induce lasting subthreshold effects that can summate with repeated attempts.

A second possibility we considered was that the stress of being exposed to a novel environment interfered with the induction of PB potentiation. With acclimation to the procedures, the rats would experience less stress, thereby reducing a possible stress-related inhibition of PB potentiation. Although we do not have a direct measure of stress in our subjects, it is well documented that exposure of an animal to an unfamiliar environment evokes behavioral and endocrine responses that are indicative of a state of high stress (Bronson, 1968; Davis et al., 1962; Hennessy & Levine, 1978; Pfister & King, 1976). It is also known that stressed rats display less LTP than nonstressed rats do (Foy, Stanton, Levine, & Thompson, 1987; Shors, Seib, Levine, & Thompson, 1989). In the present study, we noticed that the animals exhibited signs of stress (e.g., vocalizations) when they were handled in the first two recording sessions. As the animals became familiar with the experimental procedure, they became more tractable, and the incidence of PB potentiation also increased. Hence, the animals' acclimation to the experimental environment, and the concomitant reduction in the inhibitory influence of novelty stress, may be the basis of the increased incidence of PB potentiation over sessions. We refer to this possibility as the *acclimation* hypothesis.

To test the acclimation hypothesis, a group of rats were explicitly acclimated to the recording environment prior to their first PB stimulation. These animals experienced 7 days of handling and exposure to the recording chamber, without being administered PB stimulation. At the end of the 7-day acclimation period, the first PB stimulation train was given. Under these conditions, first-time PB stimulation was highly effective; lasting changes in evoked responses occurred in most (75%) of the PB stimulation attempts. These findings provide strong support for the acclimation hypothesis.

The behavioral basis of the increased incidence of PB potentiation with repeated stimulations appears, therefore, to be the reduction of novelty stress that occurs as animals adapt to an unfamiliar environment. The mechanism for this effect may involve pituitary-adrenal hormones. There is evidence that hormones in the pituitary-adrenal axis participate in the stress-related modulation of learning (Bohus, 1973; Borrell, deKloet, & Bohus, 1984; McGaugh, 1989) and hippocampal plasticity (Dubrovsky et al., 1987; Foy et al., 1987; Gold et al., 1984). In addition, we have demonstrated that manipulations of pituitary-adrenal hormones can exert profound effects on hippocampal PB

Table 2
Baseline Stimulation Voltage (V) and
Evoked Responses (mV) Across Sessions

	Stimulation (V)	Baseline (mV)
First session	6.08 ± 1.14	1.10 ± 0.18
Second session	7.53 ± 1.78	1.04 ± 0.24
Third session	5.71 ± 2.40	1.25 ± 0.23
Fourth-sixth sessions	4.16 ± 0.82	1.26 ± 0.39

potentiation. For example, the elimination of adrenal hormones, via adrenalectomy, reduces the threshold for the induction of PB potentiation in anesthetized (Diamond et al., 1989) and awake (Diamond, Bennett, & Rose, 1988) rats. We have also performed more specific analyses of the relationship between serum levels of one adrenal hormone, corticosterone, and the magnitude of PB potentiation. Preliminary data indicate that, in urethane-anesthetized rats, there is an optimal level of corticosterone (10–20 $\mu\text{g}/\text{dl}$) that is correlated with the greatest magnitude of PB potentiation; levels below 10 $\mu\text{g}/\text{dl}$ (nonstress baseline level) and greater than 20 $\mu\text{g}/\text{dl}$ (high stress level) are correlated with reduced magnitudes of PB potentiation (Bennett et al., 1989). These data indicate that corticosterone modulates hippocampal plasticity in an inverted-U function. In experiments currently underway, we are quantifying serum corticosterone levels in rats as they acclimate to the recording procedures. We are testing the hypothesis that the increase in the incidence of PB potentiation over sessions is correlated with an initially high (stress) level of serum corticosterone that decreases over sessions.

Relation to Previous Studies of Stress and Hippocampal Plasticity

Thompson and his colleagues have studied the effects of behavioral stress on LTP. In their original work, Foy et al. (1987) demonstrated that intermittent tail shocks applied to restrained animals induce an inhibitory influence on LTP. Shors et al. (1989) then identified a psychological component to the stress effect. They demonstrated that the ability of rats to control the termination of shock has a facilitatory effect on the induction of LTP: A greater magnitude of LTP occurred in animals that could escape from the aversive environment, relative to yoked control animals.

Our findings are similar to those from the Thompson group in the common observation of an inhibitory influence of stress on hippocampal plasticity. Our work differs from the aforementioned studies in terms of the nature of the stress, recording methodology, and certain aspects of the findings. Foy et al. (1987) and Shors et al. (1989) stressed rats with electrical shocks and then obtained a single recording from the hippocampus *in vitro*. In contrast, we stressed rats by exposing them to a novel environment and recorded repeatedly from the hippocampus *in vivo*. Recording from behaving rats over the course of several months enabled us to document that the stress-related inhibition of hippocampal plasticity diminishes with experience.

One difference between the findings of the two groups concerns the effects of stress on the increase in response immediately (1–2 min) following the tetanus (PTP). We have found that stress blocked the induction of both the short-term (PTP) and the long-term (PB potentiation) components. In contrast, significant PTP effects were induced by both Foy et al. (1987) and Shors et al. (1989). The most likely explanation for this difference is the degree

of high-frequency stimulation used to induce synaptic plasticity. In the present study, we used a total of 5 pulses, patterned to mimic hippocampal physiology, to generate PB potentiation. In contrast, the latter authors used more extensive stimulation (100 pulses in 1 sec) to generate LTP. The stress-induced blockade of PTP may therefore be a subtle phenomenon that is revealed only when threshold stimulation is used.

Acclimation, Learning, and Hippocampal Plasticity

The novelty-related interference with hippocampal plasticity may seem counterintuitive, and even maladaptive, when one considers that the survival of an animal may depend on its ability to learn about an unfamiliar environment. However, decades of research have provided abundant evidence that exposure of a laboratory animal or a human to an unfamiliar, and potentially threatening, environment is stressful (e.g., Davis et al., 1962; Pfister & King, 1976) and can interfere with performance (e.g., Berkun, Bialek, Kern, & Yagi, 1962; Richardson, Siegel, & Campbell, 1988; Weltman, Smith, & Egstrom, 1971).

The importance of acclimation to a novel environment as a precondition for efficient learning in behavioral paradigms was emphasized in the pioneering work of Hebb and Williams (1946) and Rabinovitch and Rosvold (1951). These authors underscored the importance of allowing animals to acclimate to the environment prior to initiating training. Experimental data supporting the importance of acclimation were provided by Bernstein and his colleagues. They reported that acclimation to human handling prior to the initiation of training significantly improved the rate at which rats learned an appetitive spatial learning task (Bernstein, 1952, 1957; Bernstein, Borda-Bossana, Atkinson, & Elrick, 1961). Similarly, Christie (1952) reported that rats with prior experience in exploring novel environments were superior in performance to a group of naive rats in a spatial learning task. Conversely, Bindra (1959) and Richardson et al. (1988) demonstrated that exposure to an unfamiliar environment interferes with a rat's responses to sensory stimulation.

Acclimation to a novel environment prior to the initiation of training is currently accepted as such an important component of learning studies that it is a standard component of many behavioral paradigms (see DiMattia & Kesner, 1984, and Fagan & Olton, 1986, for recent examples of this practice).¹ Finally, and more germane to the findings of the present study, it has been demonstrated that young rats given extensive handling prior to the initiation of physiological recordings exhibit a greater magnitude of hippocampal LTP than naive rats do (Wilson, Willner, Kurz, & Nadel, 1986).

Our demonstration of an inhibitory effect of novelty on the development of hippocampal plasticity conforms with much evidence of an inhibitory effect of novelty on behavioral performance. However, it would be incorrect to assert that learning does not occur when an animal is in

an unfamiliar environment. On the contrary, in a novel environment an animal does acquire information; but the nature of the learning differs from learning in a familiar environment in at least two ways. First, novelty can evoke a fear reaction, which results in defensive reactions to innocuous environmental stimuli (Sokolov, 1963). Under these circumstances an animal's behavior is more aligned with enhancing its survival than with acquiring information about the explicit experimenter-determined task (Mowrer, 1960; Ross, 1974). Second, the broad spectrum of cues that are potentially salient in an unfamiliar environment taxes information processing capacities, thereby interfering with behavioral performance (Kahneman, 1973; Ohman, 1979; Richardson et al., 1988). Therefore, the initial goal of an animal in a novel environment is to identify and respond to possible threats to its survival. Learning related to this goal takes precedence over, and may interfere with, the acquisition of information concerning the specific training circumstances.²

Thus, there appear to be qualitative differences between the characteristics of learning when an animal is in a novel as opposed to a familiar environment. There is also evidence that an LTP-like process occurs in some, but not all, forms of learning (McNaughton, Barnes, Rao, Baldwin, & Rasmussen, 1986; Morris, 1989; Morris et al., 1986). It is therefore possible that the form of learning that occurs when a rat is exposed to a novel or otherwise threatening environment does not involve PB potentiation-related plasticity. With acclimation to the environment, there would be an enhancement of the potential for both the development of hippocampal plasticity and hippocampal-dependent learning (see Note 1 for additional commentary relevant to this point).

An Alternative Interpretation Based on the Cognitive Map Hypothesis

Our findings, in concert with behavioral and physiological work, suggest that acclimation to an environment enhances both learning and the induction of hippocampal plasticity. However, there is an alternative interpretation of our findings and the LTP data of Wilson et al. (1986; described above). Perhaps exposure of an animal to novel circumstances produces a transient saturation of LTP-like mechanisms of plasticity. This state of hyperplasticity could occur as the hippocampus generates a spatial cognitive map (O'Keefe & Nadel, 1978). The endogenously generated saturation of hippocampal plasticity would limit the capacity for exogenous (electrical) stimulation to induce a further increase in response.

Persuasive data to the contrary have been provided by Sharp, Barnes, and McNaughton (1987) and Sharp, McNaughton, and Barnes (1985). These workers found that placement of rats in an unfamiliar environment had minimal effects on hippocampal potentials evoked by single pulse stimulation of the perforant path. Significant increases in the evoked response developed over a period of several days after the rats had been exposed to the en-

vironment. Therefore, the hippocampus does not appear to be in a hyperplastic state in the early phase of an animal's exposure to a novel environment. Only with extensive experience is there an increase in the likelihood that either endogenously induced (Sharp et al., 1987; Sharp et al., 1985) or exogenously induced (Wilson et al., 1986; present findings) plasticity will occur.

Summary and Conclusions

Rats exposed to an unfamiliar environment exhibit a low incidence of PB potentiation. With repeated PB stimulations, the incidence of PB potentiation increased significantly. Separate groups of animals were used to distinguish between the following two possible explanations of the findings: (1) The subjects acclimated to the environment, thereby reducing stress-related inhibition of hippocampal plasticity; or (2) repeated PB stimulation reduced the threshold for the induction of PB potentiation, independently of acclimation to the environment. The data support the likelihood that behavioral acclimation, rather than a threshold shift, is the basis of the increased incidence of PB potentiation over sessions.

Our findings are complementary to studies of hippocampal-dependent learning. In behavioral studies, prior acclimation to the environment facilitates learning. In our study, prior acclimation to the environment facilitated the induction of PB potentiation. Thus, the consonance between novelty stress effects on both hippocampal-dependent learning and hippocampal plasticity provides support for the hypothesis that LTP-like mechanisms underlie memory formation.

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NOTES

1. Tasks involving appetitive spatial learning typically involve the use of a period of acclimation to the training environment. In contrast, tasks that minimize the involvement of spatial components of learning and are less dependent on the integrity of the hippocampus, such as cued learning in active and inhibitory avoidance and some forms of classical conditioning (e.g., Decker & McGaugh, 1989; McCormick & Thompson, 1982; Oei & King, 1978), generally involve a reduced period of acclimation.

2. A related two-factor learning theory has been reviewed from psychological (Mowrer, 1960) and neurobiological (Weinberger & Diamond, 1987) perspectives.

(Manuscript received January 1, 1990;
revision accepted for publication April 5, 1990.)