Exposing Rats to a Predator Blocks Primed Burst Potentiation in the Hippocampus *In Vitro*

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This study evaluated the effects of acute psychological stress (cat exposure) in adult male rats on electrophysiological plasticity subsequently assessed in the hippocampus *in vitro*. Two physiological models of memory were studied in CA1 in each recording session: (1) primed burst potentiation (PBP), a low-threshold form of plasticity produced by a total of five physiologically patterned pulses; and (2) long-term potentiation (LTP), a suprathreshold form of plasticity produced by a train of 100 pulses. Three groups of rats were studied: (1) undisturbed rats in their home cage (home cage); (2) rats placed in a chamber for 75 min (chamber); and (3) rats placed in a chamber for 75 min in close proximity to a cat (chamber/stress). At the end of the chamber exposure period, blood samples were obtained, and the hippocampus was prepared for *in vitro* recordings. Only the chamber/stress group had elevated (stress) levels of corticosterone. The major finding was that PBP, but not LTP, was blocked in the chamber/stress group. Thus, the psychological stress experienced by the rats in response to cat exposure resulted in an inhibition of plasticity, which was localized to the intrinsic circuitry of the hippocampus. This work provides novel observations on the effects of an ethologically relevant stressor on PBP *in vitro* and of the relative insensitivity of LTP to being modulated by psychological stress. We discuss the relevance of these electrophysiological findings to our behavioral work showing that predator stress impairs spatial memory.

Key words: psychological stress; neuronal plasticity; memory; LTP; hippocampus; fear

Stress is known to interfere with hippocampal-dependent learning and memory in rats (Luine et al., 1994; Bodnoff et al., 1995; Conrad et al., 1996; Diamond et al., 1996b; Healy and Drugan, 1996; Krugers et al., 1997; de Quervain et al., 1998) and in people (Kirschbaum et al., 1996; Lupien and McEwen, 1997; Lupien et al., 1997). Work in our laboratory has shown that psychological stress, produced by placing rats into an unfamiliar environment (Diamond et al., 1996b) or in close proximity to a cat (Diamond et al., 1999b), impairs spatial (hippocampal-dependent) memory. We and others have also shown that stress inhibits the induction of primed burst potentiation (PBP) and long-term potentiation (LTP), two putative memory-encoding mechanisms, in the hippocampus (Shors et al., 1989; Diamond et al., 1990, 1994; Shors and Thompson, 1992; Kim et al., 1996; Xu et al., 1997). Moreover, numerous laboratories have reported that hippocampal plasticity is potently influenced by corticosterone and epinephrine, two hormones released in response to stress (Gold et al., 1984; Bennett et al., 1991; Diamond et al., 1992; Pavlides et al., 1993; Rey et al., 1994). Thus, a substantial literature now indicates that stress exerts an inhibitory influence on cognitive and electrophysiological measures of hippocampal functioning (Diamond et al., 1998; Metcalfe and Jacobs, 1998).

The original finding of a stress-induced reduction in hippocampal plasticity was reported by Foy et al. (1987). These investigators reported that there was reduced LTP in hippocampal slices obtained from rats subjected to physical stress, i.e., restraint and electric shock. An advantage of the *ex vivo* approach, i.e., a manipulation of a behaving animal followed by *in vitro* electrophysiological recordings, is that one can focus specifically on studying the intrinsic changes in hippocampal processing affected by stress, [also see Kim et al. (1996) and Pavlides et al. (1996) for *ex vivo* analyses of the role of NMDA and corticosterone receptors in mediating stress effects on LTP].

In the current work we have used a purely psychological, and ethologically relevant, stressor in an *ex vivo* analysis of stress and hippocampal plasticity. It is well known that exposing a rat to a natural predator, such as a cat, produces a profound fear response (Curti, 1935; Blanchard et al., 1990, 1998). In the present study, we stressed rats by placing them in close proximity to a cat. After the rats were exposed to the cat, slices of the hippocampus were prepared, and the capacity for electrical stimulation to evoke long-term plasticity of excitatory afferents to hippocampal CA1

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pyramidal neurons was examined. Finally, in each recording session, we used two different types of tetanizing stimulation to induce plasticity: (1) conventional LTP stimulation, consisting of a train of 100 pulses delivered in 1 sec; and (2) primed burst (PB) stimulation, consisting of a total of only five stimulus pulses presented in a pattern that mimics features of hippocampal physiology (Diamond et al., 1988). Thus, this study describes the effects of a psychological stressor (cat exposure) on two forms of plasticity (PBP and LTP) in an *ex vivo* paradigm.

Preliminary results have been presented previously (Mesches et al., 1998).

MATERIALS AND METHODS

Male Sprague Dawley rats (150–175 gm; Charles River Laboratories, Wilmington, MA) were housed in the laboratory for at least 3 d before the initiation of the experimental manipulations. Behavioral manipulations took place between 9 A.M. and 2 P.M., and the electrophysiological recordings took place between 11 A.M. and 4 P.M. Animals in one group ($n = 7$ animals and 9 slices) were placed individually into a clear Plexiglas box (25 × 10 × 10 cm), which had numerous 7-mm-diameter ventilation holes. The box containing the rat was then put into a sound-attenuating chamber (71 × 61 × 61 cm) for 75 min (chamber/control). Rats in a second experimental group ($n = 8$ animals and 11 slices) were each placed in the Plexiglas box and subsequently put into the chamber. For this group, however, an adult female cat moved about freely within the chamber for the entire 75 min period (chamber/stress). The Plexiglas enclosure protected the rat from possible attack but still allowed it to experience the cat through visual, auditory, and olfactory cues. Rats in a third group ($n = 7$ animals and 9 slices) served as a control for the influence of removal of the subjects from their home environment. These rats were not exposed to either the chamber or the cat and remained undisturbed in their home cages before hippocampal slice preparation (home cage/control).

All rats were decapitated at the end of the 75 min chamber period or at the corresponding time of the day for the home cage control group. The brain was rapidly removed from the skull, and a sample of trunk blood was obtained for subsequent analysis of serum corticosterone levels. Corticosterone levels were analyzed by radioimmunoassay by an investigator who was blind to the experimental treatments. Transverse hippocampal slices, 400 μm thick, were prepared using conventional methods (Diamond et al., 1988) and were placed in a recording chamber on a nylon net and bathed with isotonic medium at a temperature of 33–34°C. The slice medium was composed of (in mM): 124 NaCl, 3.3 KCl, 2.5 $CaCl_2$, 2.0 $MgCl_2$, 1.2 KH_2PO_4, and 10 glucose. The medium was saturated with 95% O_2 and 5% CO_2 to maintain the pH at 7.4, and the top surface of the slices was exposed to the humidified gas mixture. Extracellular recordings were made from the CA1 pyramidal cell layer using glass micropipettes filled with the slice medium (resistance, 1.5–2.5 MΩ). Bipolar stimulating electrodes, made from a twisted pair of 37-μm-diameter Formvar-insulated nichrome wires, were placed in stratum radiatum to evoke positive field EPSPs with superimposed population spikes. Stimuli were delivered, and evoked responses were recorded using a microcomputer and EPmax software (Eclectic Engineering Studio, Denver, CO). All slices included in this experiment generated population spikes of at least 5 mV and demonstrated a reduction of population spike amplitude (i.e., paired pulse inhibition) in response to the second of a pair of stimuli presented 20 msec apart.

Evoked responses were produced by delivering a single test pulse (150 μsec duration) every 30 sec during baseline and post-tetanic (PBP and LTP) periods. Baseline responses were established using a stimulation intensity sufficient to elicit a population spike ~2 mV in amplitude. After a 10 min baseline period, primed burst stimulation was given, consisting of a single stimulus pulse followed 170 msec later by a high-frequency (200 Hz) burst of four pulses (five pulses total). After the PB stimulation, responses to test pulse stimuli were recorded every 30 sec for 30 min.

At the end of the 30 min post-PB stimulation period, the stimulation current was adjusted, if necessary, to return the response amplitude to its original baseline. After a new 10 min baseline was established, LTP stimulation was given, consisting of 100 pulses delivered at 100 Hz. Responses to subsequent test stimuli were then delivered every 30 sec for another 30 min. The intensity of the tetanic (PBP and LTP) stimulation was the same as that used for the test stimulation pulses. Averaged population spike amplitudes during the 10 min PBP or LTP baseline period were compared with those in the period from 21–30 min after PBP or LTP stimulation (t test). Group differences were analyzed by ANOVA and *post hoc* Bonferroni corrected t tests.

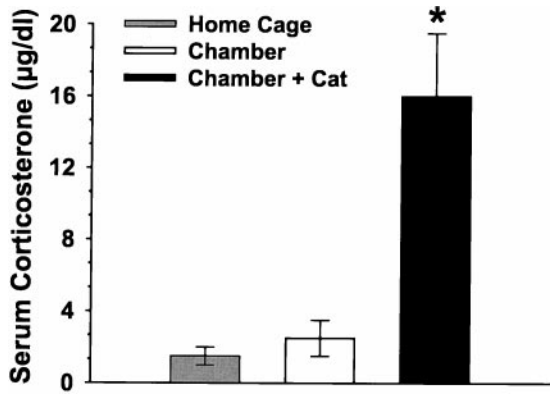

Figure 1. Cat exposure increased serum corticosterone levels. Blood samples obtained from rats exposed to a cat for 75 min exhibited greater corticosterone levels than samples obtained from rats that were either killed directly out of their home cage or had spent 75 min in the chamber without the cat. $^*p < 0.01$, Bonferroni corrected t test.

Table 1. Baseline electrophysiological parameters were not different across groups

Group	Baseline response (mV)	Stimulation (μA)	Paired pulse ratio @ 20 msec
Home cage control	2.29 ± 0.11	58.5 ± 11.93	0.16 ± 0.10
Chamber control	2.11 ± 0.09	79.9 ± 17.8	0.10 ± 0.04
Chamber with cat	2.00 ± 0.09	65.1 ± 10.0	0.10 ± 0.04

RESULTS

Exposing rats to a cat elicited a significant elevation of their serum corticosterone in blood samples obtained at the time of decapitation, compared with the home cage control group. In contrast, rats placed in the chamber without the cat had serum corticosterone levels that were not different from the home cage group (ANOVA, $p < 0.01$; Fig. 1). The presence of the cat, therefore, and not placement in the chamber alone, was stressful to the rats.

Baseline population spike amplitudes and the stimulus intensities necessary to elicit baseline responses were not different among the groups. Similarly, there was no difference among the groups in the degree of inhibition of the population spike on the second evoked response in the paired pulse test (ANOVA, $p > 0.1$). These findings are consistent with other work showing that stress has no effect on baseline measures of cellular excitability (Shors and Thompson, 1992; Diamond et al., 1994). These data are presented in Table 1.

In contrast to the similarity among the groups in baseline electrophysiological measures, there was a striking difference among the groups in terms of their capacity to develop synaptic plasticity. PB stimulation produced a significant increase in the magnitude of the population spike in seven of nine (78%) slices from the home cage (control) rats and in eight of nine (89%) slices from the chamber animals. However, PB stimulation produced a significant increase in the magnitude of the population spike in only 2 of 11 (18%) slices obtained from the rats that had

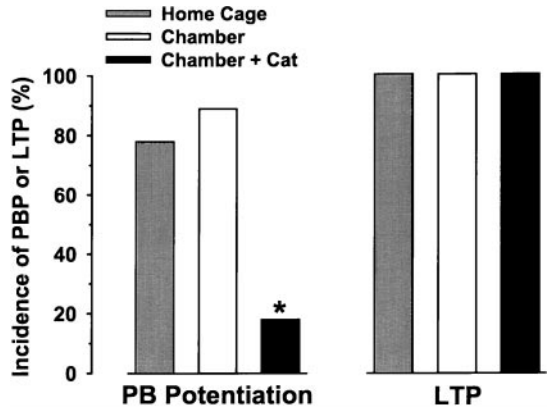

Figure 2. Predator stress reduced the incidence of PBP (*left side*) but not LTP (*right side*). Whereas PBP occurred in most of the slices from home cage and chamber control rats, PBP occurred very rarely in slices obtained from rats exposed to the cat. LTP, however, occurred in all slices in all groups, thereby showing no differential sensitivity to the stress manipulation. *Significant difference in the incidence of PBP among the three groups (χ^2, $p < 0.01$).

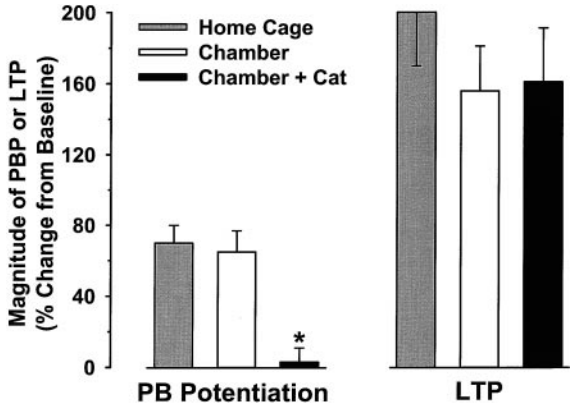

Figure 3. Predator stress reduced the magnitude of PBP (*left side*) but not LTP (*right side*). PB stimulation produced a smaller magnitude of enhancement than did LTP stimulation. More importantly, PBP was significantly reduced in slices obtained from rats exposed to the cat compared with home cage and chamber-exposed rats. LTP, by contrast, was unaffected by the stress manipulation. *$p < 0.01$, Bonferroni corrected *t* test.

been exposed to the cat (Fig. 2). This difference in the incidence of PB potentiation among the groups was significant ($\chi^2 = 12.2$; 2 df; $p < 0.01$; Fig. 2, *left side*). In addition, the response enhancement after PB stimulation was equivalent in the home cage and chamber exposure groups (70 ± 10 vs 60 ± 12%), but the chamber/stress group showed no significant enhancement of response (3 ± 10%; ANOVA, $p < 0.01$; Fig. 3, *left side*). Taken together, these findings indicate that there was a significant reduction in the incidence and magnitude of PBP in slices obtained from rats exposed to the cat for 75 min before decapitation.

The LTP findings contrasted with the PBP findings. The same slices that exhibited a stress-induced blockade of PBP were unaffected in their expression of LTP. All slices in all groups developed a lasting increase in response amplitude after LTP stimulation (100% incidence of LTP in all three groups; Fig. 2, *right side*), and the magnitudes of LTP in the three groups were not significantly different (ANOVA, $p > 0.1$; Fig. 3, *right side*).

DISCUSSION

The findings of this study replicate and extend previous work on the stress-induced inhibition of hippocampal plasticity. In the original work on stress and plasticity, Foy et al. (1987) showed that when rats were restrained and shocked there was a reduction in the magnitude of hippocampal LTP assessed *in vitro*. Subsequent studies from this group have provided an extensive characterization of the inhibitory effects of physical stress on hippocampal somatic (population spike) and dendritic (field EPSP) plasticity (Shors et al., 1989; Shors and Thompson, 1992; Kim et al., 1996). In parallel with the work on physical stress and LTP, other studies have shown that psychological stress can block LTP (Xu et al., 1997) and a low-threshold form of LTP, referred to as PBP, *in vivo* (Diamond et al., 1990, 1994, 1998). The current work brings together components of each of these approaches and in the process provides novel insight into the modulation of hippocampal plasticity by stress.

The primary finding is that psychological stress, produced by an instinctual fear of a predator, resulted in such a profound inhibitory influence on the hippocampus that plasticity was blocked when the recordings subsequently took place *in vitro*. This high degree of durability of stress effects on synaptic plasticity provides strong evidence that hippocampal functioning is highly susceptible to disruption by increased emotionality.

The significance of the stress-induced impairment of hippocampal functioning has been addressed in our earlier work on stress and hippocampal-dependent memory (Diamond et al., 1996b) and also by Metcalfe and Jacobs (1998) in their review of the animal and human literature. The common theme in these studies is that stress impairs hippocampal-related processing, suggesting that the amnestic and memory-distorting effects of stress may result from impaired hippocampal processing. Recently, we used the same stressor used in the current work, i.e., exposing rats to a cat, to evaluate the effects of stress on hippocampal-dependent (spatial) memory. We found that rats that were exposed to a cat exhibited impaired spatial working memory (Diamond et al., 1999b). Other studies have also shown that hippocampal-specific learning and memory are impaired by acute and chronic stress in rats (Luine et al., 1994; Bodnoff et al., 1995; Conrad et al., 1996; Diamond et al., 1996b; Healy and Drugan, 1996; Krugers et al., 1997; de Quervain et al., 1998) and in people (Kirschbaum et al., 1996; Lupien et al., 1997). The complementary findings in cognitive and electrophysiological studies support the hypothesis that stress-induced impairments of PBP and spatial memory are regulated by common neuroendocrine mechanisms.

The basis of the stress effects observed here remains to be determined, but one likely candidate for mediating the *ex vivo* effects of stress on PBP is corticosterone. Studies of hippocampal plasticity *in vivo* and *in vitro* have shown that there is a negative linear relationship between stress levels of corticosterone and the magnitude of hippocampal plasticity (Foy et al., 1987; Bennett et al., 1991). That is, as levels of corticosterone increase there is a decrease in the magnitude of LTP and PBP, and an enhancement of long-term depression. Further analysis of the entire physiological range of corticosterone (low, intermediate, and high stress levels) reported that the corticosterone plasticity curve is an inverted U-shaped function, with peak levels of LTP and PBP at intermediate (low stress) levels of corticosterone (Diamond et al., 1992; Kerr et al., 1994). Behavioral studies also show that elevated levels of corticosterone, or stress-related activation of corticoste-

rone (glucocorticoid) receptors, can impair hippocampal-dependent learning and memory (Wolkowitz et al., 1990; Arbel et al., 1994; Luine, 1994; Newcomer et al., 1994; Bodnoff et al., 1995; Conrad et al., 1997; de Quervain et al., 1998; Oitzl et al., 1998). Thus, the findings of the current work are consistent with the idea that stress levels of corticosterone generated by predator exposure initiated a chain of events, including protein synthesis (Karst and Joels, 1991; Joels et al., 1995), which resulted in an impairment of cognitive and electrophysiological measures of hippocampal function.

This work also illustrates the problem of methodological influences on the expression of the stress-induced modulation of hippocampal functioning. Conventional LTP stimulation, i.e., tetanizing trains of $\geq$100 pulses, produce such a high degree of depolarization that this form of plasticity is less sensitive to modulation by behaviorally relevant variables than is PBP. Although studies have shown that LTP can be affected by stress (Shors et al., 1989; Shors and Thompson, 1992; Kim et al., 1996) and hormonal manipulations (Gold et al., 1984; Kerr et al., 1994; Pavlides et al., 1994, 1995; Rey et al., 1994), our findings are consistent with other work showing that the induction of LTP is less sensitive than PBP to modulation by behaviorally relevant influences such as aging (Moore et al., 1993), stress (Diamond et al., 1999a), and neuromodulators (Corradetti et al., 1992; Diamond et al., 1996a). Although psychological stress produces an inhibitory bias against the development of hippocampal plasticity, the strength of this bias appears to be insufficient to significantly affect the physiological processes initiated by LTP stimulation [see Kim and Yoon (1998) for discussion of interactions among stress, depolarization, and the threshold for the induction of plasticity].

In our experimental paradigm, PB stimulation was always given before LTP stimulation. Therefore, the possibility must be considered that PB stimulation somehow altered the responsiveness of CA1 to the subsequent LTP stimulation. Although theoretically possible, this scenario is unlikely for the following reasons. First, we have shown that ineffective PB stimulation has no effect on the response to tetanizing stimulation delivered later in that session (Diamond et al., 1990). Second, in cases in which ineffective tetanizing stimulation has been shown to affect the response to subsequent stimulation, the ineffective stimulation reduced, rather than sensitized, the magnitude of LTP (Huang et al., 1992). The simplest explanation for the absence of an effect of stress on LTP in our study is the relative insensitivity of LTP to modulation by psychological stress.

It is also important to consider the possibility that other LTP stimulation paradigms may be more sensitive to modulation by behaviorally relevant influences than the LTP stimulation protocol used here. For example, some studies have shown that stress can affect the magnitude of LTP produced by multiple bursts of electrical pulses delivered in a theta-related pattern of stimulation (Shors and Thompson, 1992). Our conclusions on the insensitivity of LTP to modulation by stress implicate conventional "nonpatterned" trains of stimulation as perhaps the most insensitive means with which to study the effects of behavioral manipulations on synaptic plasticity.

In summary, we exploited a rat's instinctual fear of a cat to produce a pure psychological stress response. Although this fear response did not affect general excitability in the hippocampus, it did result in an impairment of hippocampal plasticity when assessed using the PB stimulation paradigm. Whereas PBP was readily induced in control slices, PBP rarely occurred in slices obtained from rats exposed to the cat. However, more prolonged tetanizing stimulation generated equivalent magnitudes of LTP in all experimental groups. Taken together, these results show that psychological stress produced profound and lasting changes in the capacity for the intrinsic circuitry of the hippocampus to express plasticity. However, consistent with our previous studies, inhibition of hippocampal plasticity by psychological stress was observed only when threshold level, physiologically patterned, stimulation was used.

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