

Research report

# Neonatal exposure to a novel environment enhances the effects of corticosterone on neuronal excitability and plasticity in adult hippocampus

Bende Zou<sup>a,d</sup>, Golijeh Golarai<sup>b</sup>, John A. Connor<sup>b</sup>, Akaysha C. Tang<sup>a,b,c,\*</sup>

<sup>a</sup>Department of Psychology, Logan Hall, Room 162, The University of New Mexico, Albuquerque, NM 87131, USA

<sup>b</sup>Department of Neurosciences, The University of New Mexico, Albuquerque, NM 87131, USA

<sup>c</sup>Department of Computer Science, The University of New Mexico, Albuquerque, NM 87131, USA

<sup>d</sup>National Laboratory of Biomembrane and Membrane Biotechnology, College of Life Sciences, Peking University, Beijing 100871, People's Republic of China

Accepted 3 April 2001

## Abstract

Electrophysiological studies have shown that activation of glucocorticoids receptors (GRs) influences neuronal excitability and activity dependent synaptic plasticity. In developmental studies, early life stimulation such as neonatal handling results in an up-regulation of glucocorticoid-receptor (GR) binding in the hippocampus that persists into adulthood. It is, therefore, hypothesized that early environment-induced changes in receptor sensitivity to corticosterone (CORT) might have functional effects on adult neuronal excitability and synaptic plasticity. To test this hypothesis, we exposed rats daily from post-natal days 1–21 to a non-home environment for 3 min. When the animals became adults, we studied the effects of glucocorticoid hormone corticosterone (CORT) on population spike (PS) amplitude and long-term potentiation of population spikes (PS-LTP) *in vitro* in the hippocampal CA1 region following activation of the Schaffer collateral fibers. Bath application of CORT reduced PS amplitude and subsequent induction of PS-LTP. This inhibitory effect of CORT was significantly greater in the slices from the novelty exposed rats (Novel) than the control rats that remained in their home cage (Home). Inhibition of population spike amplitude during CORT perfusion was  $28.0 \pm 5.3\%$  of baseline in Novel slices, and  $9.1 \pm 4.4\%$  in Home slices. CORT pre-exposure (20 min) also inhibited the subsequent induction of PS-LTP in Novel slices by  $57.7 \pm 17.7\%$  and by  $7.5 \pm 12.1\%$  in Home slices. These results provide electrophysiological evidence that neonatal novelty exposure results in functional increases in receptor sensitivity to CORT that enhances the inhibitory effects of CORT on field CA1 neuronal excitability and plasticity. © 2001 Elsevier Science B.V. All rights reserved.

*Theme:* Development and regeneration

*Topic:* Hormones and development

*Keywords:* Corticosterone; Novelty; Population spike; CA1; Hippocampus; LTP

## 1. Introduction

Postnatal environmental manipulations can result in long-lasting changes within the hypothalamic–pituitary–adrenal (HPA) axis and in the negative feedback control of the HPA axis [38,23,25,42,24,2]. Handling rat pups during infancy has been shown to result in long-lasting up-

regulation of hippocampal glucocorticoid receptor (GR) binding, which mediates the negative feedback control of CORT release [23,19,22,21,39]. These handled animals also show less age-related cognitive decline than controls [23], measured by performance in the Morris water maze task [27]. Although it is well known that CORT plays an important role in modulating learning and memory [17,16,14,44,7] and that behavioral stress, exogenous application of corticosterone (CORT), and its agonists/antagonists can all influence hippocampal dependent learning [6,3,28,5,8,29–31,26], the cellular mechanisms connecting receptor up-regulation to enhanced hippocampal

\*Corresponding author. Tel.: +1-505-277-4025; fax: +1-505-277-4946.

E-mail addresses: akaysha@unm.edu (A.C. Tang), <http://kongzi.unm.edu> (A.C. Tang).

dependent learning are not known. One possibility is that receptor up-regulation may enhance CORT's modulation of neuronal excitability and plasticity. Therefore, we hypothesized that postnatal environmental manipulations might facilitate adult learning through an enhanced CORT modulation of excitability [36,41,13,10,11] and long-term potentiation (LTP) [7,4,37,12,40,33,35,32] in the hippocampus.

We have previously shown that postnatal environmental manipulation, such as daily exposure of neonatal rats to a novel environment for 3 min results in enhanced hippocampal dependent spatial learning in the water maze task [43,44]. Here, combining the same neonatal novelty procedure with *in vitro* electrophysiology, we present evidence that subtle early environmental manipulation leads to long lasting enhancement in CORT modulation of hippocampal neuronal excitability and plasticity during adulthood. The relationship between these cellular and behavioral effects of postnatal environmental manipulation will be discussed.

## 2. Methods and materials

### 2.1. Experimental animals

Six pregnant Long Evan hooded rats were housed in our animal facility for 11 days prior to giving birth (Harlan Sprague–Dawley Company, Indianapolis, IN). Twenty-five pups (17 male and 8 female) born of the these dams (litter size ranged 5–9) were included in this study. Pups were housed with the dams until weaning on postnatal day 21. Post weaning, the dams and pups were housed individually in translucent plastic cages (20×20×40 cm) on 12 h light–dark cycle, and given food and water *ad lib*. Brain slice electrophysiology experiments were performed on 61 slices from these 25 rats during adulthood (7–8 months).

### 2.2. Neonatal novelty exposure

At postnatal day 1, approximately one half of each litter was randomly assigned to the Novel and the other half to the Home conditions (split-litter design). Group membership was marked using a toe clipping procedure. We modified the classical handling procedure [15] to reduce the number of behavioral factors involved from three (maternal separation, experimenter handling, and exposure to a new environment) to one—the exposure to a new environment alone [44]. In our novelty exposure procedure (Fig. 1a), first the dam was removed from the home cage. Secondly, the Novel and Home pups were identified by an experimenter using the toe markings. The identified Novel rats were then placed in a new cage for their 3 min exposure and subsequently returned to their home cage. This was followed by the return of the dam to the litter. Note, both the Novel and Home pups were separated from

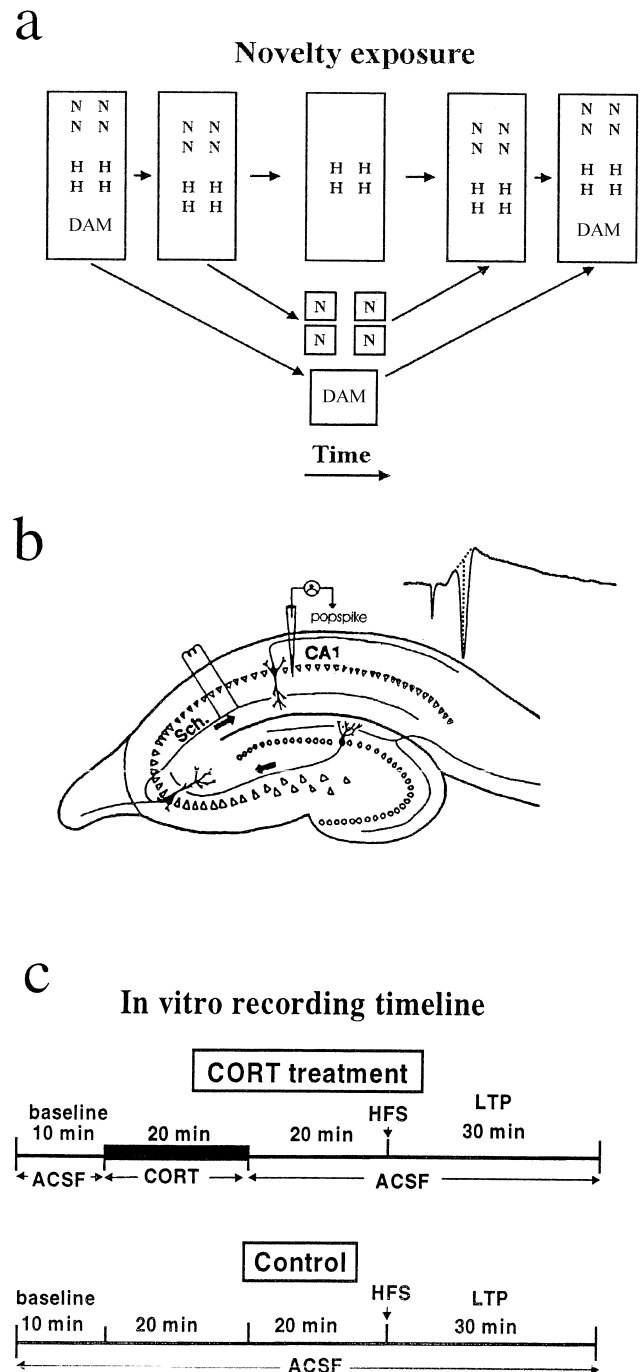


Fig. 1. (a) Novel pups (N) were exposed to a novel cage for 3 min every day from postnatal days 1–21, while the Home pups (H) stayed in the home cage. Both the Home and Novel pups were touched by the experimenter and separated from the dam. (b) A schematic graph of coronal slice of the hippocampus shows the stimulation and recording sites. (c) A timeline for *in vitro* electrophysiological recordings in CORT-treated and control slices.

the dam and each time a Novel pup was touched by an experimenter during the transfer to and away from the novelty environment, a Home pup was matched by a similar touch by the experimenter. A total of 13 Novel and 12 Home rats were studied.

### 2.3. Slice preparation

In vitro brain slice experiments were performed double-blind at 7–8 months of age. All rats were sacrificed at a set time of day (approximately 11:00 h). Rats were anesthetized deeply with halothane and decapitated. The brain was quickly removed and placed in artificial oxygenated cerebrospinal fluid (ACSF) with 5% CO<sub>2</sub>/95% O<sub>2</sub> at approximately –4°C. ACSF consisted of (in mM): NaCl 124.0; KCl 2.5; KH<sub>2</sub>PO<sub>4</sub> 1.2; CaCl<sub>2</sub> 2.4; MgSO<sub>4</sub> 1.3; and glucose 10. Transverse hippocampal slices (400 μm) were cut using a Vibroslice (Campden Instruments), and incubated in oxygenated ACSF at room temperature for at least 1 h before recording. During recording, slices were submerged in a standard recording chamber (Medical System Corp.) and perfused with oxygenated ACSF (2.5 ml/min) at 32°C. All data included in this study were collected within 10 h of dissection.

### 2.4. Stimulation and recording

For afferent stimulation, a concentric bipolar stimulating electrode was placed in CA1 stratum radiatum, and constant current pulses (0.1–0.2 mA, 0.2 ms duration) were delivered at 0.1 Hz (test pulses). Field potentials were recorded using a glass microelectrode filled with 3 M NaCl (tip resistance: 1–3 MΩ) and placed in the stratum pyramidale layer of CA1 (Fig. 1b). An input/output function was obtained using test pulses at 16 different intensity levels ranging from minimum intensity required to generate a detectable excitatory post-synaptic potential (EPSP) to that required for evoking the maximum population spike amplitude. Stimulus intensity was then adjusted to evoke a population spike 50% of maximum amplitude. Experiments proceeded only if field potential amplitudes were stable for at least 10 min. Signals were band-pass filtered (3 Hz–3 KHz), amplified (Brownlee model 440), digitized, and then analyzed using the Labview data acquisition and analysis environment (National Instrument). LTP was induced by high frequency stimulation (HFS: 10 trains of 20 test pulses at 200 Hz, one each 2 s).

We bath-applied 100 nM CORT (in ACSF+0.009% ethanol) for 20 min [41] (Fig. 1c) to study CORT's inhibitory effect on excitability and plasticity [11]. The actual concentration of CORT in the bath can be significantly lower because heating of the bath chamber to 32°C can cause ethanol to rapidly evaporate. A concentration of 100 nM is the lowest concentration at which a clear reduction of population spike amplitude could be reliably observed in our laboratory and is also a concentration considered physiologically relevant (personal communication with Mary Dallman). In a few Home slices tested, we did not observe any noticeable ethanol effect. After testing potential ethanol effect by comparing the ACSF and ACSF/0.009% ethanol conditions, we found no significant differences between the two conditions. We

therefore pooled slices recorded under ACSF and ACSF + 0.009% ethanol in the subsequent analysis.

### 2.5. Data analysis

Population spike amplitudes (Fig. 1b) were measured using an average over six successive trials. The HFS-induced PS-LTP was measured as percentage change from baseline 30 min following HFS. All data are expressed as mean and standard error of the mean (SEM). Statistical comparison were made using paired or unpaired *t*-test, or ANOVA with repeated measures as appropriate.

## 3. Results

The following analysis was based on slices combined from both male and female rats as no gender difference in CORT's effect was found. Population spike amplitude, latency, and duration were not significantly different between Home and Novel slices (see Table 1). Fig. 1c summarizes protocols for assessing acute CORT effects. To compare the sensitivity of population spikes to CORT modulation in Novel and Home slices, we monitored evoked population spike amplitudes in CA1 before, during, and after a 20 min bath application of CORT (100 nM). CORT produced a reduction in population spike amplitude (Fig. 2a) in both Home and Novel slices. Typically, this inhibitory effect first became apparent at about 5 min after CORT onset and reached maximum after approximately 20 min of CORT superfusion and was reversed after washing with ACSF for 20–30 min. At 19 min after CORT onset, population spike amplitude in Home slices were reduced to 90.9±4.4% of the baseline ( $P < 0.05$ ,  $n = 7$ , two-tailed). In Novel slices, CORT elicited a greater reduction in population spike amplitude of 72.1±5.3% of the baseline ( $P < 0.05$ ,  $n = 9$ , two-tailed). CORT suppression of population spike amplitude differed significantly between the Novel and Home slices (ANOVA with repeated measure  $P < 0.05$ ,  $n = 16$ ).

Application of HFS reliably induced LTP of the population spikes in both Novel and Home slices (Fig. 3a top). The first train of HFS (200 Hz, 100 ms) to Schaffer collaterals was sufficient to saturate LTP. This LTP was greatly reduced by bath application of 50 μM APV starting at 20 min before HFS and continuing during LTP maintenance, leaving only a residual LTP (Fig. 3a bottom and

Table 1  
The basic value of population spikes in CA1 of home and novel rats ( $n = 61$ )

	Latency (ms)	Duration (ms)	Amplitude (mV)	<i>n</i>
Novel	3.92±0.10	3.12±0.06	3.24±0.20	29
Home	3.79±0.11	3.10±0.09	3.20±0.14	32
<i>P</i>	>0.20	>0.20	>0.20	

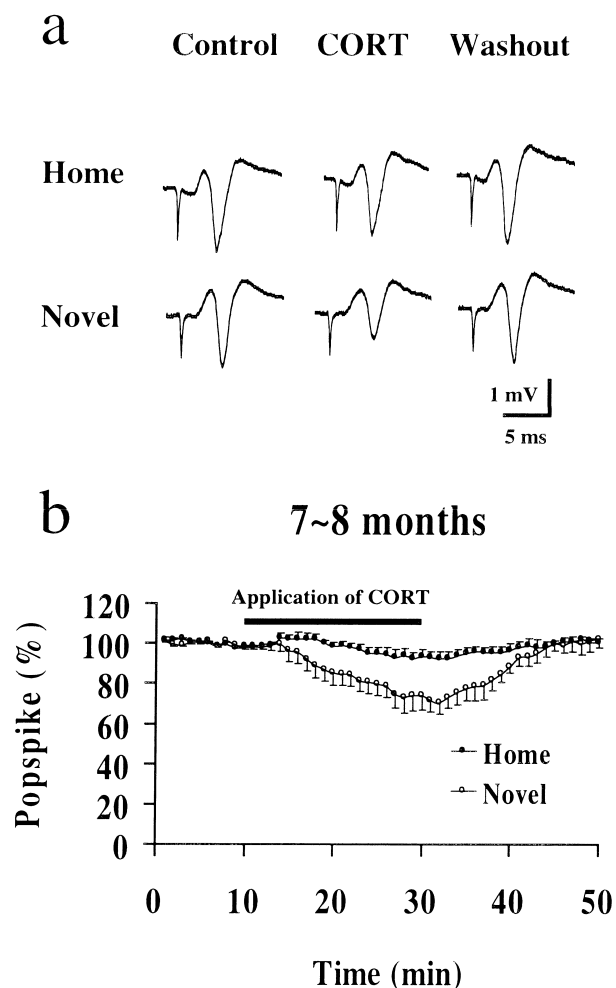


Fig. 2. Bath application of 100 nM CORT resulted in a greater inhibition of population spike in Novel than in Home slices. (a) These example of population spikes were recorded before, during and after 20 min CORT perfusion in Novel and Home slices. (b) Time course of CORT effect demonstrates the significantly greater reduction of population spike amplitude in Novel slices.

Fig. 3b). Potentiation of population spike amplitude was subsequently reversed by application of low frequency stimulation (2 Hz, 900 pulses; data not shown). To compare modulation of PS-LTP in Novel and Home slices by CORT, population spikes were recorded under two conditions: with and without CORT exposure prior to LTP induction. To dissociate CORT's inhibitory effect on PS-LTP from an acute effect on excitability, slices were washed with ACSF for 20–30 min after the 20 min CORT perfusion until the acute inhibitory effect of CORT was reversed (Fig. 2b). After re-stabilization of the population spike amplitude for 10 min, HFS was applied to induce LTP. Elapsed time from the beginning of recording to LTP induction was matched between CORT treated and control slices (Fig. 1c bottom).

In Novel slices, PS-LTP was significantly reduced from  $231.0 \pm 21.0\%$  (without CORT pre-exposure) to  $174.3 \pm 14.4\%$  (with CORT pre-exposure) ( $P < 0.05$ ,  $n =$

12, two-tailed). Similarly, post-tetanic potentiation of population spike (PS-PTP) was reduced from  $259.3 \pm 26.2\%$  (without CORT pre-exposure) to  $198.3 \pm 18.0\%$  (with CORT pre-exposure) ( $P < 0.01$ ,  $n = 12$ , two-tailed). In contrast, CORT pre-exposure did not produce significant suppression of PS-LTP in Home slices, with PS-LTP equal to  $183.4 \pm 12.7\%$  without CORT pre-exposure vs.  $175.9 \pm 11.5\%$  with CORT pre-exposed ( $P > 0.20$ ,  $n = 13$ , two-tailed) and PS-PTP equal to  $200.9 \pm 8.7\%$  without CORT pre-exposure vs.  $205.5 \pm 16.5\%$  with CORT pre-exposure ( $P > 0.20$ ,  $n = 13$ , two-tailed). CORT pre-exposure induced suppression of PS-PTP and PS-LTP was significantly greater in Novel compared to Home Slices (ANOVA with repeated measure,  $P < 0.05$ ,  $n = 25$ , Fig. 3c,d).

We also measured fEPSP slope from the same traces as population spikes. The trend of CORT effect on this fEPSP measure were similar but smaller compared to the effect on population spikes and the effects on popspike/fEPSP ratio were qualitatively similar to those found on population spikes. In Novel slices, PS-LTP/fEPSP ratio was significantly reduced from  $174.1 \pm 12.9\%$  (without CORT pre-exposure) to  $143.2 \pm 9.7\%$  (with CORT pre-exposure) ( $P < 0.05$ ,  $n = 12$ , one-tailed). Similarly, post-tetanic potentiation of population spike (PS-PTP) to fEPSP ratio was reduced from  $188.6 \pm 167.5\%$  (without CORT pre-exposure) to  $167.5 \pm 15.4\%$  (with CORT pre-exposure) ( $P = 0.185$ ,  $n = 12$ , one-tailed) but the effect was not significant. In contrast, CORT pre-exposure did not produce significant suppression of PS-LTP/fEPSP ratio in Home slices, with PS-LTP/fEPSP equal to  $148.4 \pm 9.5\%$  without CORT pre-exposure vs.  $140.9 \pm 10.9\%$  with CORT pre-exposed ( $P > 0.20$ ,  $n = 13$ , two-tailed) and PS-PTP/fEPSP equal to  $166.6 \pm 17.2\%$  without CORT pre-exposure vs.  $167.5 \pm 15.4\%$  with CORT pre-exposure ( $P > 0.20$ ,  $n = 13$ , two-tailed). CORT pre-exposure induced suppression of PS-LTP/fEPSP ratio was greater in Novel compared to Home Slices (ANOVA with repeated measure,  $P = 0.077$ ,  $n = 25$ , nearly significant).

## 4. Discussion

### 4.1. Neonatal novelty exposure produces long-term increase in hippocampal sensitivity to CORT

We studied whether subtle neonatal stimulation can influence the effects of CORT on synaptic transmission and long term synaptic plasticity in field CA1 of the hippocampus in adult rats. Our results show that a brief 3 min daily exposure to a novel environment during the first 3 weeks of life can, in fact, result in long-lasting changes in CORT modulation of neuronal excitability and plasticity within the hippocampus. Specifically, neonatal stimulation significantly enhanced the net inhibitory effect of the CORT on neuronal excitability, measured by population

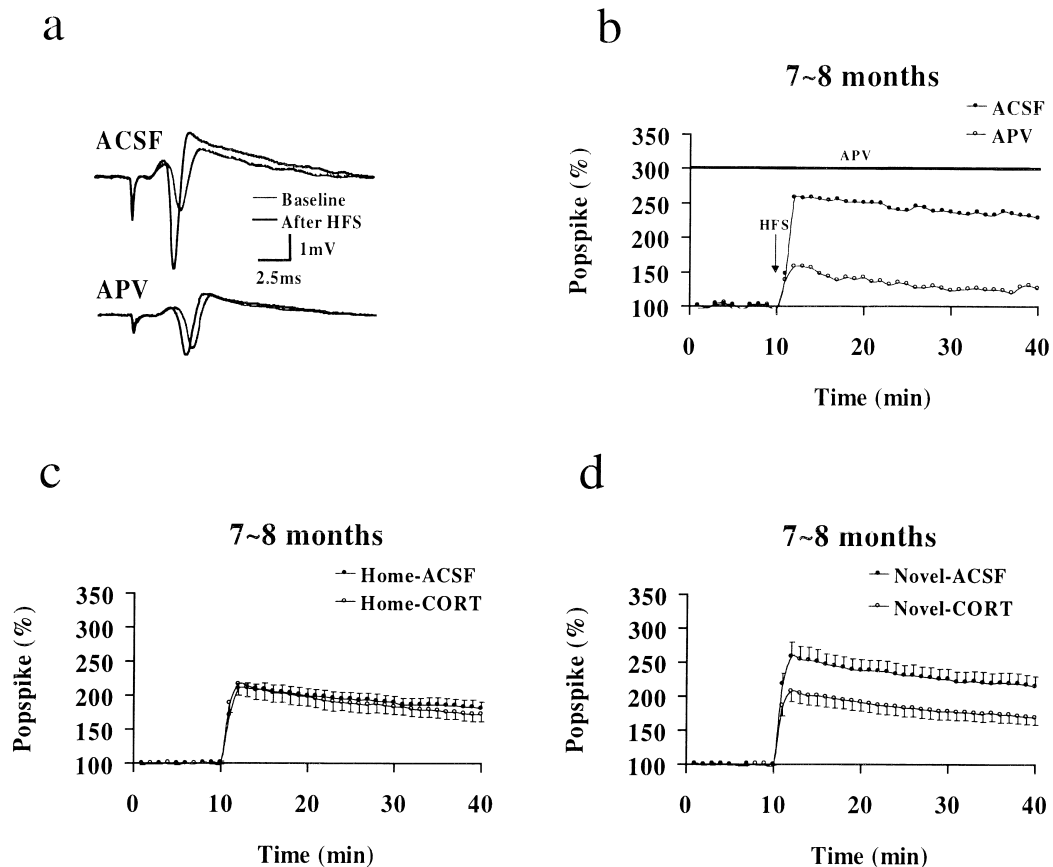


Fig. 3. Expression of LTP following CORT pre-exposure was significantly reduced in Home vs. Novel slices. (a) PS-LTP is largely NMDA dependent, as shown by typical population spike responses before and after HFS in ACSF and in 50  $\mu$ M APV. (b) Time course of LTP in ACSF (filled circle) and during bath application of 50  $\mu$ M APV (open circle). (c) CORT pre-exposure had no effect on PS-LTP in Home rat slices. (d) Pre-exposure to CORT reduced PS-LTP in slices from novelty exposed rats.

spike amplitude. CORT reduced population spike amplitude in slices from Novel rats three times more than slices from rats that were not exposed to the novel environment (Fig. 2b). Furthermore, exposure to stress-level CORT prior to inducing LTP led to a reduction in population spike LTP in Novel, but not control rats (Fig. 3c,d). Both results suggest that neonatal stimulation can lead to an increased sensitivity to CORT modulation during adulthood. Because the amount of maternal separation and experimenter contact were equalized between the Novel and Home rats, the enhanced CA1 sensitivity to CORT among the novelty exposed rats can be attributed to neither maternal separation nor experimenter handling, but to the exposure to the novel non-home environment.

#### 4.2. Possible physiological role of an increase in CORT modulation of hippocampal excitability

By using a high concentration of CORT (100 nM), we intended to study the differential inhibitory effects of stress-induced hormone release on hippocampal excitability and plasticity between the novelty-exposed and control rats. We found that CORT's inhibitory effect on CA1

population spikes was enhanced by neonatal novelty exposure. As the hippocampus exerts an excitatory effect on the HPA axis [18,9], an increase in circulating CORT concentration can lead to reduction in hippocampal activation which in turn reduces HPA output. Thus, one consequence of neonatal novelty exposure is an increased effectiveness of the hippocampal-mediated feedback control of HPA axis [18,9].

Neonatal handling, another early life stimulation procedure similar to our novelty exposure, was shown to result in an up-regulation of GRs in the hippocampus of both young adult and aged animals [23,19,22,21,39]. It has been suggested that the functional significance of this up-regulation is to mediate a more effective negative feedback control of the HPA axis [38,23,20] during stress. Although it has been known that activation of GRs can have an inhibitory effect on hippocampal neuronal excitability [36,41,13,10], it remained an open question whether this handling-induced GR up-regulation actually plays a physiological role. Our finding that stress-level CORT does, indeed, produce greater inhibition of hippocampal activity in neonatal novelty-exposed rats provides the first electrophysiological evidence supporting a

possible role for early experience-induced increase in receptor sensitivity to CORT in mediating the negative feedback control of the HPA axis.

#### 4.3. CORT modulation of adult LTP is altered by neonatal novelty-exposure

We found that a 20 min transient exposure to stress-level CORT prior to applying an LTP induction protocol, led to greatly reduced PS-LTP in the Novel but not the Home rats (Fig. 3c). This result suggests that PS-LTP in Novel slices are more sensitive to CORT modulation than in Home slices. Our study differs from previous *in vitro* study on CORT modulation of hippocampal LTP [37] in that we attempted to separate CORT's acute effect on excitability from its delayed effect on the induction of PS-LTP. Instead of inducing LTP during CORT perfusion, we allowed CORT's acute effect on population spike amplitude to reverse before the LTP protocol was given. It is possible that a more severe reduction of PS-LTP occurs if the LTP induction protocol is delivered during CORT exposure. In the current study, this possibility has not yet been examined in the interest of obtaining a clear time line between the two effects.

The effect of CORT on PS-LTP has been studied in CA1 [37,35,34], CA3 [32], and DG [40,33] of the hippocampus in normal control rats. These studies were carried out primarily through systemic injection of CORT followed by *in vivo* [12,40,33,32,34] or *in vitro* [35] recordings, or bath perfusion of CORT during *in vitro* recording in slices [37]. In contrast to these studies performed on unconditioned animals, our study was designed to investigate whether there is any difference in CORT's effects between the unconditioned and neonatal novelty-exposed rats. We showed that early life event can enhance the sensitivity of PS-LTP to CORT modulation.

As PSPs contained population spikes which could have subtle effects on the slope of the initial slope of fEPSPs, we are more confident about the population spike amplitude measure than about the measure of initial fEPSP slopes. With this in mind, we report that CORT treatment on Novel slices affected the ratio between population spike amplitude and initial slope of fEPSPs in the same direction (reduction) but with smaller effect size and reduce statistical significance. It is also important to point out that changes in the population spike that are independent of the fEPSP can result from either alterations of postsynaptic voltage-gated channels or the efficacy of feed-forward inhibition [1]. The current study does not distinguish between the two mechanisms.

How increased sensitivity to CORT during stress might affect learning is not known. One possibility is that increased CORT inhibition of PS and PS-LTP could reduce interference from non-task related neuronal activation. If optimal learning consists of selectively updating synaptic strengths that specifically encode task-related

information, then global non tasks-related activation due to stress in a new learning situation may interfere with memory consolidation [7]. An increased sensitivity of PS-LTP to CORT could dampen such interference more effectively during stress induced release of CORT.

## 5. Uncited reference

[45]

## Acknowledgements

We thank C.F. Stevens, M. Dallman and P. Stanton for comments and discussions, T. Verstyne for assistance, and G. Cowan for his generous support.

## References

- [1] W. Abraham, B. Gustafsson, H. Wigstrom, Long-term potentiation involves enhanced synaptic excitation relative to synaptic inhibition in guinea-pig hippocampus, *J. Physiol.* 394 (1987) 367–380.
- [2] H. Anisman, M. Zharia, M. Meaney, Z. Merali, Do early-life events permanently alter behavioral and hormonal responses to stressors?, *J. Dev. Neurosci.* 16 (3/4) (1998) 149–164.
- [3] I. Arbel, T. Kadar, M. Sibermann, A. Levy, The effects of long-term corticosterone administration on hippocampal morphology and cognitive performance of middle-aged rats, *Brain Res.* 657 (1994) 227–235.
- [4] M. Bennet, D. Diamond, M. Fleshner, G. Rose, Serum corticosterone level predicts the magnitude of hippocampal primed burst potentiation and depression in urethane-anesthetized rats, *Psychobiology* 19 (4) (1991) 301–307.
- [5] S. Bodnoff, A. Humphrey, J. Lehmann, D. Diamond, G. Rose, M. Meaney, Enduring effects of chronic corticosterone treatment on spatial learning, synaptic plasticity and hippocampal neuropathology in young and mid-aged rats, *J. Neurosci.* 15 (1995) 61–69.
- [6] S. Dachir, T. Kadar, B. Robinson, A. Levy, Cognitive deficits induced in young rats by long-term corticosterone administration, *Behav. Neural Biol.* 60 (1993) 103–109.
- [7] E. Dekloet, M. Oitzl, M. Joels, Stress and cognition: are corticosteroids good or bad guys?, *Trends Neurosci.* 22 (10) (1999) 422–426.
- [8] D. Diamond, B. Branch, M. Fleshner, The neurosteroid dehydroepiandrosterone sulfate (dheas) enhances hippocampal primed burst, but not long-term, potentiation, *Neurosci. Lett.* 202 (3) (1996) 204–208.
- [9] J. Herman, W. Cullinan, Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis, *Trends Neurosci.* 20 (1997) 78–84.
- [10] M. Joels, E. de Kloet, Effects of glucocorticoids and norepinephrine on the excitability in the hippocampus, *Science* 245 (1989) 1502–1505.
- [11] M. Joels, E. Dekloet, Control of neuronal excitability by corticosteroid hormones, *Trends Neurosci.* 15 (1992) 25–30.
- [12] D. Kerr, A. Huggett, W. Abraham, Modulation of hippocampal long-term potentiation and long-term depression by corticosteroid receptor activation, *Psychobiology* 22 (2) (1994) 123–133.
- [13] D. Kerr, L. Campbell, S.-Y. Hao, P. Landfield, Corticosteroid

- modulation of hippocampal potentials: increased effect with aging, *Science* 245 (1989) 1505–1509.
- [14] J. Kim, K. Yoon, Stress: metaplastic effects in the hippocampus, *Trends Neurosci.* 21 (12) (1998) 505–509.
- [15] S. Levine, Infantile experience and resistance to physiological stress, *Science* 126 (1957) 405.
- [16] S. Lupien, B. McEwen, The acute effects of corticosteroids on cognition: integration of animal and human model studies, *Brain Res. Rev.* 24 (1997) 1–27.
- [17] B. McEwen, R. Sapolsky, Stress and cognitive function, *Curr. Opin. Neurobiol.* 5 (1995) 205–216.
- [18] B. McEwen, E. De Kloet, W. Rostene, Adrenal steroid receptors and actions in the nervous system, *Physiol. Rev.* 66 (1986) 1121–1188.
- [19] M. Meaney, D. Aitken, The effects of early postnatal handling on hippocampal glucocorticoid receptor concentrations: temporal parameters, *Dev. Brain Res.* 22 (1985) 301–304.
- [20] M. Meaney, R. Sapolsky, B.S. McEwen, The development of the glucocorticoid receptor system in the rat limbic brain. I. ontogeny and autoregulation, *Dev. Brain Res.* 18 (1985) 159–164.
- [21] M. Meaney, D. Aitken, S. Bodnoff, L. Iny, R. Sapolsky, The effects of postnatal handling on the development of the glucocorticoid receptor systems and stress recovery in the rat, *Prog. Neuropsychopharm. Biol. Psychiat.* 7 (1985) 731–734.
- [22] M. Meaney, D. Aitken, S. Bodnoff, L. Iny, J. Tararewicz, R. Sapolsky, Early postnatal handling alters glucocorticoid receptor concentrations in selected brain regions, *Behav. Neurosci.* 99 (1985) 765–770.
- [23] M. Meaney, D. Aiken, S. Bhatnager, C. Vanberkel, R. Sapolsky, Effects of neonatal handling on age-related impairments associated with the hippocampus, *Science* 239 (1988) 766–769.
- [24] M. Meaney, J. Diorio, D. Francis, J. Widdowson, P. Laplante, C. Caldji, S. Sharma, J. Seckl, P. Plotsky, Early environmental regulation of forebrain glucocorticoid receptor gene expression: Implications for adrenocortical responses to stress, *Developmental neuroscience* 18 (1-2) (1996) 49–72.
- [25] M. Meaney, J. Mitchell, D. Aitken, S. Bhatnagar, S. Bodnoff, L. Iny, A. Sarrieau, The effects of neonatal handling on the development of the adrenocortical response to stress: implications for neuropathology and cognitive deficits in later life, *Psychoneuroendocrinology* 16 (1-3) (1991) 85–103.
- [26] M. Mesches, M. Fleshner, K. Herman, G. Rose, D. Diamond, Exposing rats to a predator blocks primed burst potentiation in the hippocampus in vitro, *J. Neurosci.* 19 (1999) RC18.
- [27] R. Morris, G. Garrud, J. Rawlings, J. O'Keefe, Place navigation impaired in rats with hippocampal lesions, *Nature* 297 (1982) 681–683.
- [28] J. Newcomer, S. Craft, T. Hershey, K. Askins, M. Bardgett, Glucocorticoid-induced impairment in declarative memory performance in adult humans, *J. Neurosci.* 14 (1994) 2047–2053.
- [29] M. Oitzl, E. Deklot, Selective corticosteroid antagonists modulate specific aspects of spatial orientation learning, *Behav. Neurosci.* 106 (1992) 62–71.
- [30] M. Oitzl, M. Flutterm, E. Dekloet, Acute blockade of hippocampal glucocorticoid receptors facilitates spatial learning in rats, *Brain Res.* 797 (1) (1998) 159–162.
- [31] M. Oitzl, M. Flutterm, W. Sutanto, E. Dekloet, Continuous blockade of brain glucocorticoid receptors facilitates spatial learning and memory in rats, *Eur. J. Neurosci.* 10 (12) (1998) 3759–3766.
- [32] C. Pavlides, B. McEwen, Effects of mineralocorticoid and glucocorticoid receptors on long-term potentiation in the CA3 hippocampal field, *Brain Res.* 851 (1-2) (1999) 204–214.
- [33] C. Pavlides, Y. Watanabe, B. McEwen, Effects of glucocorticoids on hippocampal long-term potentiation, *Hippocampus* 3 (2) (1993) 183–192.
- [34] C. Pavlides, A. Kimura, A. Magarinos, B. McEwen, Type-I adrenal-steroid receptors prolong hippocampal long-term potentiation, *Neuroreport* 5 (18) (1994) 2673–2677.
- [35] C. Pavlides, S. Ogawa, A. Kimura, B. McEwen, Role of adrenal steroid mineralocorticoid and glucocorticoid receptors in long-term potentiation in the CA1 field of hippocampal slices, *Brain Res.* 738 (2) (1996) 229–235.
- [36] D. Pfaff, M. Silva, J.M. Weiss, Telemetered recording of hormone effects on hippocampal neurons, *Science* 172 (1971) 394–395.
- [37] M. Rey, E. Carlier, M. Talmi, B. Soumireuourat, Corticosterone effects on long-term potentiation in mouse hippocampal slices, *Neuroendocrinology* 60 (1) (1994) 36–41.
- [38] R. Sapolsky, M. Meaney, B. McEwen, The development of the glucocorticoid receptor system in the rat limbic brain. III. negative-feedback regulation, *Dev. Brain Res.* 18 (1985) 169–173.
- [39] A. Sarrieau, S. Sharma, M. Meaney, Postnatal-development and environmental-regulation of hippocampal glucocorticoid and mineralocorticoid receptors, *Dev. Brain Res.* 43 (1) (1988) 158–162.
- [40] M. Smriga, H. Saito, N. Nishiyama, Hippocampal long- and short-term potentiation is modulated by adrenalectomy and corticosterone, *Neuroendocrinology* 64 (1) (1996) 35–41.
- [41] C. Vidal, W. Jordan, W. Zieglgansberger, Corticosterone reduces the excitability of hippocampal pyramidal cells in vitro, *Brain Res.* 383 (1986) 54–59.
- [42] C. Walker, K. Scribner, C. Cascio, M. Dallman, The pituitary–adrenocortical system of neonatal rats is responsive to stress throughout development in a time-dependent and stressor-specific fashion, *Endocrinology* 128 (1991) 1385–1395.
- [43] A. Tang, L. Alvarado. Enhancing spatial episodic memory through early experience. *Cognitive Neurosci. Abs.*, 1999.
- [44] A. Tang, Neonatal exposure to novel environment enhanced hippocampal-dependent memory function during infancy and adulthood, *Learn. Memory, Special Issue*, 2001.
- [45] D. de Quervain, B. Roozendaal, J. McGaugh, Stress and glucocorticoids impair retrieval of long-term spatial memory, *Nature* 394 (1998) 787–790.