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**TITLE: Corticosterone Administration to Promote Fear Memory
Forgetting Process in an Animal Model of PTSD**

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14. ABSTRACT (200 words) Activation of glucocorticoid receptor signaling and its subsequent alterations has been implicated in the pathophysiological fear response to stress and the pathogenesis of stress-associated psychiatric disorders such as posttraumatic stress disorder (PTSD). To further examine the association between alterations in central glucocorticoid receptor signaling and the occurrence of stress-induced psychiatric symptoms, the present study, utilizing a learned helplessness stress model in rats, examines whether glucocorticoid receptor signaling activation shortly before or after stress might prevent the occurrence of stress-induced physical and behavioral abnormalities such as exaggerated acoustic startle response (ASR) and reduced body weight gain. Rats subjected to restraint/tail shock for three days have been shown to develop a long-lasting elevated ASR and reduced body weight gain, compared to non-stressed control animals. In this study, the glucocorticoid receptor agonist, corticosterone (3 mg/kg), will be administered 30 min before or after exposure of the animals to the stress protocol. Acoustic startle response (ASR), plasma corticosterone levels and body weight will be measured on Day -1 (baseline readings) and on Days 7, 14 and 21 after completion of the stress protocol. The glucocorticoid antagonist RU 486 was administered to determine the specificity of therapeutic efficacy of corticosterone.					
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Table of Contents

	<u>Page</u>
Introduction.....	4
Body.....	4
Key Research Accomplishments.....	12
Reportable Outcomes.....	12
Conclusion.....	12
References.....	13
Appendices.....	N/A

INTRODUCTION

Subject: It has been observed in normal subjects that forgetting is a spontaneous and gradual process in which previous memories are no longer readily retrievable from brain memory storage. The rate of forgetting is generally a function of time since an event was experienced (Wixted, 2004). However, in PTSD patients, vivid flashbacks of traumatic memories occur even years after the traumatic incident, indicating that there is a failure of the forgetting process in the PTSD brain. Is there any way to promote the forgetting process in a PTSD subject? Emerging evidence suggests that systemic administration of corticosterone can enhance the memory forgetting process in animals and in healthy humans (de Quervain et al., 1998; Aerni et al., 2004). However, whether administration of corticosterone can also reduce fear memory flashbacks in PTSD patients is currently unknown. We hypothesize that administration of corticosterone prior to or shortly after a period of intense, repeated stress will promote the traumatic memory forgetting process. In this report we discuss the first step in testing this hypothesis – determination of a reduction in the enhanced acoustic startle reflex (ASR) in our animal model of PTSD, which is a measure of traumatic memory retrieval.

Purpose: Our immediate objective is to use an animal model of PTSD developed in our laboratory to investigate the effectiveness of administration of corticosterone prior to or shortly after a period of intense, repeated stress, in preventing the retrieval of, and promote the forgetting of, fearful memories. The use of a pharmacologic intervention to promote the memory forgetting process requires that it be introduced in an appropriate time window and in an optimized dose in order to obtain maximum efficacy without inducing adverse side effects. The experiments proposed will measure changes in ASR in stressed and control animals before and after administration of corticosterone. In addition, some animals will receive a corticosterone receptor (CR) antagonist to control for any non-cortisone effects.

Scope:

- **Innovation:** This study will provide information about the cellular mechanisms underlying PTSD and fill a knowledge gap in the current research on PTSD. Such knowledge may facilitate the development of novel pharmacological interventions for the treatment of PTSD.
- **Intervention:** Administration of novel pharmacologic interventions may help to prevent as well as treat PTSD. More specific interventions provide treatment while minimizing side effects.
- **Application:** Novel pharmacologic interventions have the potential for broad use both in military populations (those on active duty, reservists and veterans) and in civilian populations exposed to traumatic stress (natural disasters, vehicle crashes, etc.).

BODY

Task 1: Animal Protocol Approvals

Announcement of Concept Award PT073670 to He Li, M.D., Ph.D.(PI) and Lei Zhang, M.D. and Robert J. Ursano, M.D. (CoPIs), was made on January 3, 2008. The Certificate of Environmental Compliance for this project was awarded by the USUHS Environmental Compliance Officer on January 15, 2008 and the PI Assurance Document was signed January 15, 2008. An animal protocol was submitted to the USUHS IACUC on February 8, 2008 and approved on April 24, 2008. A copy of the IACUC approved animal protocol was submitted to the USAMRMC ACURO for review; ACURO approval was issued May 12, 2008. All animal experiments have been done in accordance with IACUC and ACURO approved protocols. A

total of 401 rats have been used for the experiments included in the current report.

Task 2: Administration of the Stress Protocol and ASR Measurements

In our previous research supported by the DoD (DAMD17-00-1-0110), we successfully established an animal model of PTSD in which an inescapable tail-shock protocol is used to administer traumatic stress to rats. We have verified that long-lasting behavioral and physiological alterations, known to simulate the symptoms of PTSD observed and reported by us and others (table1) (Jiang et al., 2009;Braga et al., 2004;Manion et al., 2007;Ottenweller et al., 1992;Servatius et al., 1995).

PTSD in Humans	Inescapable tail-shock model of stress in rats
Weight loss	Suppressed feeding and body weight loss
Difficulty falling or staying asleep, nightmares	Altered sleep patterns
Psychomotor numbness	Persistent behavioral abnormalities i.e. suppressed open-field activity, longer hanging wire latencies
Poor concentration; memory deficits	Deficits in escape/avoidance learning and learning of an appetitive task
Hypervigilance and/or exaggerated startle response	Exaggerated startle

Table 1. Comparison of Symptoms of PTSD in Humans to Dysfunction Related to Stress in Rats

The stress protocol was administered to young adult male Sprague Dawley rats weighing ~150 gm on the first day of stress. Animals were housed 2 to a cage and allowed to acclimate to the USUHS Animal Facility for at least 5 days. No animals died or were injured as a result of exposure to the stress protocol. Stress exposure consisted of a 2-h per day session of immobilization and tail-shocks for three consecutive days. We stressed animals in the morning (between 0800 and 1200). They were restrained in a plexiglass tube, and 40 electric shocks (1 mA, 3 s duration) were applied at varying intervals (140–180 s). This stress protocol was adapted from the ‘learned helplessness’ paradigm in which animals underwent an aversive experience under conditions in which they could not perform any adaptive response (Seligman and Maier, 1967;Seligman and Beagley, 1975). The rats were stressed for three consecutive days because it had been previously demonstrated that repeated stress sessions for three days were more effective than a single stress session in producing physiological and behavioral abnormalities associated with depression and anxiety disorders (Ottenweller et al., 1989;Servatius et al., 1995b). Additional stress sessions do not appear to produce greater physiological and behavioral changes (Ottenweller et al., 1992;Ottenweller et al., 1989).

The ASR test was conducted with a Startle Response Acoustic Test System (Coulbourn Instruments, Columbus, Ohio, USA). The system consisted of four movement sensitive platforms in a sound-attenuated chamber, though only one platform was used at a time. A subject’s movements in response to stimuli were transduced into analog signals by a

piezoelectric unit attached to the platforms. These signals were then digitized and stored by a computer. All acoustic stimuli were given by a loudspeaker mounted 24 cm above the test cage. To minimize the effects of handling and stress on drug testing, animals were allowed to acclimate to the startle chamber for 3 days before experiments. The startle baselines were then tested for each animal on Day -1 before they experienced the stress protocol. During testing, rats were individually placed in an animal holder (E05-15, Coulbourn Instruments, Columbus, Ohio, USA), which was then placed on the movement-sensitive platform within the chamber. A ventilating fan built into the chamber provided background noise. Following a 3-min acclimation period, animals were exposed to six types of stimulus trials: 100 and 110 dB alone, both 100 and 110 dB with pre-pulse (84dB), pre-pulse alone and no stimulus. Each trial type was presented eight times. Trial types were presented in random order to avoid order effects and habituation. Inter-trial intervals ranged randomly from 15 to 25s. Animals were tested during their dark cycle; during the experiments only a red light was provided in the dark room. ASR testing of all animals took place on Day 10 and 21 following completion of the stress protocol.

Animals' maximum startle responses were averaged within trial type. Trials during which no stimuli were presented were used to control for normal subject movements on the platform. Since acceleration (a) of the rat's body indicates startle in the ASR paradigm, yet the transducer in the ASR apparatus is a force (F) transducer, the measure of startle output by the apparatus is a multiple of the animal's body mass (m), according to Newton's Second Law, $F = ma$. During the twenty one day course of the experiment, the animals grow from 50g to 200g, and each animal grows at a somewhat different rate, hence body mass is a confounding variable which must be adjusted, which we did by dividing out body mass, leaving acceleration as our measure of startle. Startle response during each trial type was derived by subtracting peak platform force on the no-stimulus trials from peak platform force in response to specific stimuli, and then dividing by the animal's body mass. The result from this calculation represents absolute amplitude of ASR to the stimulus (e.g., 100 dB, 100 dB with pre-pulse, 110 dB, 110 dB with pre-pulse). The ASR amplitude tested each time was finally represented as "% of baseline", which was calculated using the equation: % of baseline = (absolute amplitude / baseline amplitude) 100%. For each test day, ANOVAs or t-test for repeated measures were performed on startle amplitudes with factors of stress status and drug dosage. The Dunnett test was used to assess significant post-hoc differences between individual groups. The data were represented as mean $\pm$ S.E.M.

As hypothesized, the key behavioral phenotype of our model of PTSD is that traumatic stress induces a delayed and enhanced ASR to 100dB sound stimuli on day 14 and day 21 after the termination of the stress protocol (ANOVA repeated measures $F(1, 54) = 9.007$, $p < 0.01$). When the percentages of maximum values of ASR to the intensity of sound at 100dB were adjusted for body mass, as described above, the analysis from further t tests indicated that adjusted ASRs were significantly enhanced on day 14 ($p < 0.01$) and day 21 ($p < 0.05$) but not on day 7. (Fig. 1) between stressed versus controlled groups shown in Fig. 1.

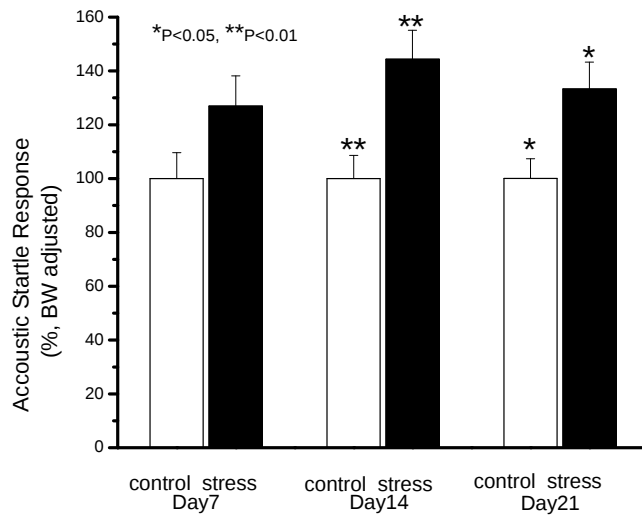


Figure 1. The effect of traumatic stress on ASR. Mean $\pm$ S.E.M. of peak startle amplitude (100 dB, body weight adjusted, represented as % of the ASR baseline) for groups of stress and control measured 7, 14 and 21 days following three days stress protocol. Asterisks (*) indicate significant differences between groups ($p<0.05$) and (**) indicate $p<0.01$. $n=24$ control group; $n=32$ stress group.

It is also noticed that the body weight gain is not only a biological indicator for examining the impact of traumatic stress but was also a biomarker for evaluating the efficacy of pharmacological intervention in our previous research (Jiang, et al 2009). Thus, as shown in the figure 2, animals, after 3 days of the stress of restraint and inescapable tail-shock, had a reduction in their normal gain in body weight. This reduction persisted during the stress period, and, although gain returned to normal following stress, net body weight remained lower on 1, 7, 14 and even 21 day following stress.

Fig 2 A

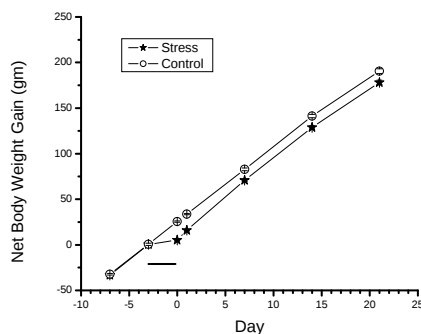


Fig. 2 B

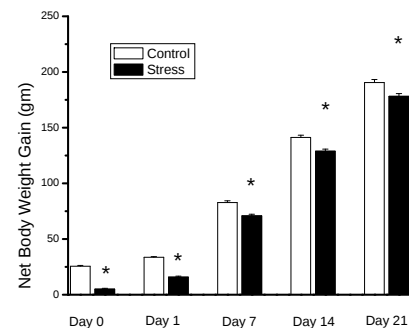


Figure 2. The effect of stress on average growth rate following the stress. (A). Means of net body weight gain of different groups were plotted against the days post-stress. The body weight gain was measured on the days before stress and immediately following each stress session, and on subsequent days up to Day 21 following stress.

(B). The comparison of net body weight gains of stress and control groups measured 0, 1, 7, 14 and 21 days following stress. Asterisks (*) indicate significant differences between groups (* $p < 0.01$). Day 0 Control $n = 61$, Stress $n = 52$; Day 1 Control $n = 60$, Stress $n = 52$; Day 7, 14 and Day 21 control $n = 69$, stress $n = 60$.

Task 3: Administration of corticosterone pre-stress to determine its effect on ASR. As proposed, corticosterone (3 mg/kg and 0.3 mg/kg) was administered to stressed and control animals thirty minutes prior to administration of the stress protocol on three consecutive days. Baseline acoustic startle measurements for stressed and control animals were determined on Day -1 preceding exposure to the stress protocol. Baseline measurements of body weight were made on Day -1 preceding stress both as a physiological measure and as a metric for balancing the groups. After the third and final exposure to stress, animals were weighed immediately after stress and again on Days 1, 7, 14 and 21 post stress. For each test day, ANOVAs and/or t-tests for measures were performed on net weight gain and averaged growth rate with the factors of stress status and drug dosage. Dunnett's test was used to assess significant post-hoc differences between individual groups. The data were represented as mean $\pm$ S.E.M in Figure 3.

Task 4: Administration of corticosterone post-stress to determine its effect on ASR. As proposed, corticosterone (3mg/kg) was administered to stressed and control animals thirty minutes after administration of the stress protocol on three consecutive days. Baseline acoustic startle measurements (obtained from tail or trunk blood samples) for stressed and control animals were determined on Day -1 preceding exposure to the stress protocol. Body weight measurements were also recorded. The same measurements were made on Day 21 following completion of the stress protocol. Additional experiments involving post-stress administration of corticosterone have indicated that post-stress treatment with corticosterone has a short term efficacy (14 days after stress) and has no significant effect in attenuating the exaggerated ASR in this animal model of PTSD 21 days after stress, as shown in figure 3.

Summary of Experimental Results of Task 3 and Task 4:

1. The effect of administration of corticosterone prior to, or immediately following, stress on stress-enhanced ASR.

As proposed, the effect of the stress protocol and administration of the drug (3 mg/kg corticosterone) or vehicle on ASR was first examined. Consistent with previous reports, exposure to three-day restraint/tail shock increased the ASR amplitude on Day 14 following stress $p < 0.05$ (Figure 1). **The vehicle injection has no significant impact on the basal acoustic startle response in comparison to non- stressed control animals.** The effect of stress on ASR continued to be observed on Day 21 following stress (Figure 1), indicating that the enhanced startle response was a long-lasting effect of this stress protocol. **The corticosterone administration alone was without effect on ASR amplitude, similar to that in control animals (on day 14, $p > 0.5$).** **Corticosterone (3mg/kg) administration prior to stress attenuated the exaggerated ASR induced by the stress of three days restraint and inescapable tail-shock in PTSD animal model.** Data analysis further revealed that corticosterone (3mg/kg) injected immediately following stress has short term efficacy in decreasing the stress-induced enhancement of ASR, in comparison to the long term effect

induced by the administration of this compound (3mg/kg) prior to stress (Figure 3 and 4). These results indicate that the optimized time window for corticosterone intervention is 30 minute before stress. In addition, when the initial data for corticosterone at 3mg/Kg were analyzed, after body mass was corrected, the diminution in ASR just reached statistical significance ($p < 0.05$) at 21 days post-stress. Hence the corticosterone dose of 3mg/Kg was taken to be the threshold in this stress /ASR paradigm. Taking the corticosterone dose of 3mg/Kg to be the threshold in this stress /ASR paradigm obviated the purpose in testing animals at the planned corticosterone dose of 1mg/Kg. Hence the time, effort, 24 animals, and materials scheduled for the 1mg/Kg corticosterone trials were devoted to trials at 3mg/Kg corticosterone, particularly as needed in conjunction with RU486.

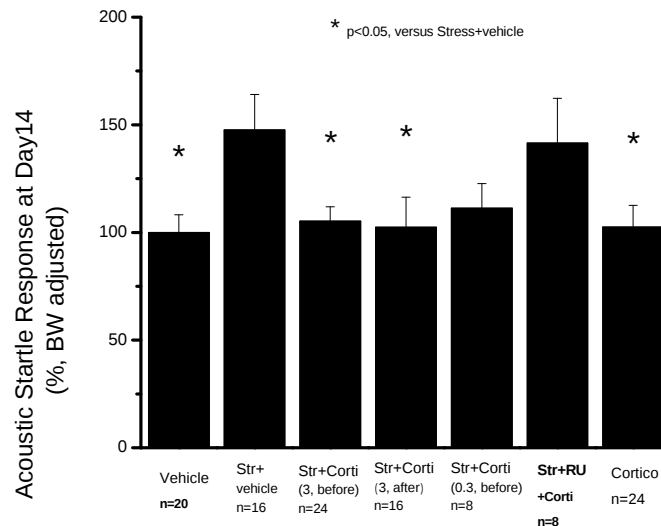


Figure 3. Mean $\pm$ S.E.M. of peak startle amplitude (body weight adjusted, represented as % of the baseline ASR) for groups of vehicle alone, stress plus vehicle, stress plus corticosterone (3mg/kg, 30 minutes before stress), stress plus corticosterone (3mg/kg, 30 minutes after stress), stress plus corticosterone (0.3mg/kg, 30 minutes before stress), stress plus RU486 and corticosterone (3mg/kg) injection and corticosterone (3mg/kg) injection alone measured 14 days following treatments. Asterisks (*) indicate significant differences between groups ($p < 0.05$) and (**) indicate $p < 0.01$.

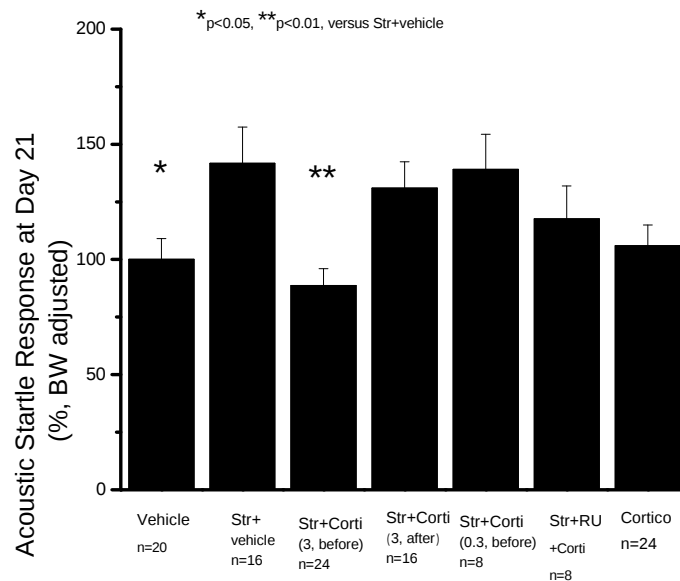


Figure 4. Mean $\pm$ S.E.M. of peak startle amplitude (body weight adjusted, represented as % of the baseline ASR) measured 21 days after the following treatments: of vehicle alone, stress plus vehicle, stress plus corticosterone (3mg/kg, 30 minutes before stress), stress plus corticosterone (3mg/kg, 30 minutes after stress), stress plus corticosterone (0.3mg/kg, 30 minutes before stress), stress plus RU486 and corticosterone (3mg/kg), and corticosterone (3mg/kg) alone. Asterisks (*) indicate significant differences between groups ($p<0.05$) and (**) indicate $p<0.01$.

2. Administration of corticosterone prior to stress in relation to the body weight of the stressed animals. The subjects we used in this study were young adult rats (125-150g) when the experiments began. At this stage, the animals' body weight increased very quickly (5-7 g/day). As illustrated by Figure 2, exposure to three-day inescapable tail-shock significantly decreased the body weight gain in stressed animals ($p<0.01$), resulting in a lower body weight than that of their control counterparts. This effect remained as long as 21 days following stress (Figure 2A and B). Corticosterone treatment in control animals did not produce a significant effect on body weight gain at any day of the measurement (Figure 5). Stressed animals receiving corticosterone treatment (3mg/kg or 0.3 kgmg/kg) 30 minutes prior to stress (pretreatment) gained no more weight than stressed animals treated with vehicle on day 21 (Figure 5B4). Likewise, corticosterone treatment immediately following stress (post-treatment) did not compensate for the retardation of body weight gain in comparison to that in control group during the 21 days observation period. Thus, while weight gain was retarded during stress under all conditions, weight gain was constant and non-compensatory in all groups post stress (Figure 4 and 5, $p>0.05$ at all time points).

Fig 5. A

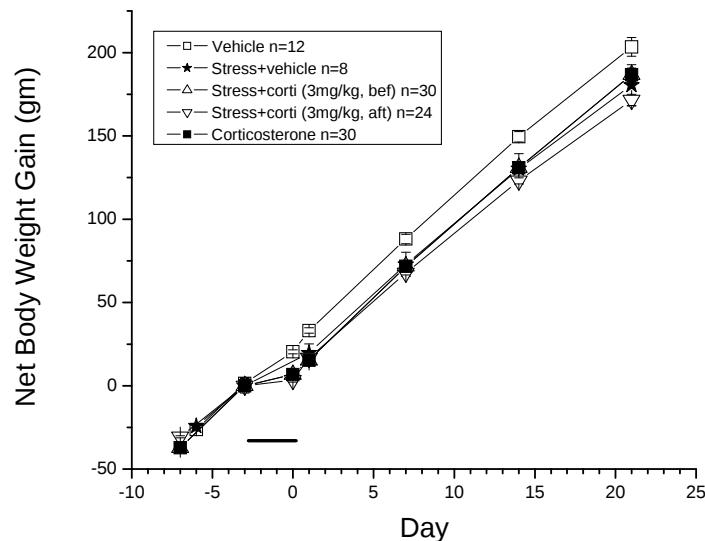


Figure 5 A. The effects of corticosterone on the net body weight gain. Means $\pm$ S.E.M of net weight gains of vehicle, stress plus vehicle, stress plus corticosterone (3mg/kg, 30 minutes before stress), stress plus corticosterone (3mg/kg, 30 minutes after stress) and corticosterone (3mg/kg) injection groups (measured immediately following treatments and 1, 7, 14 and 21 days following treatments).

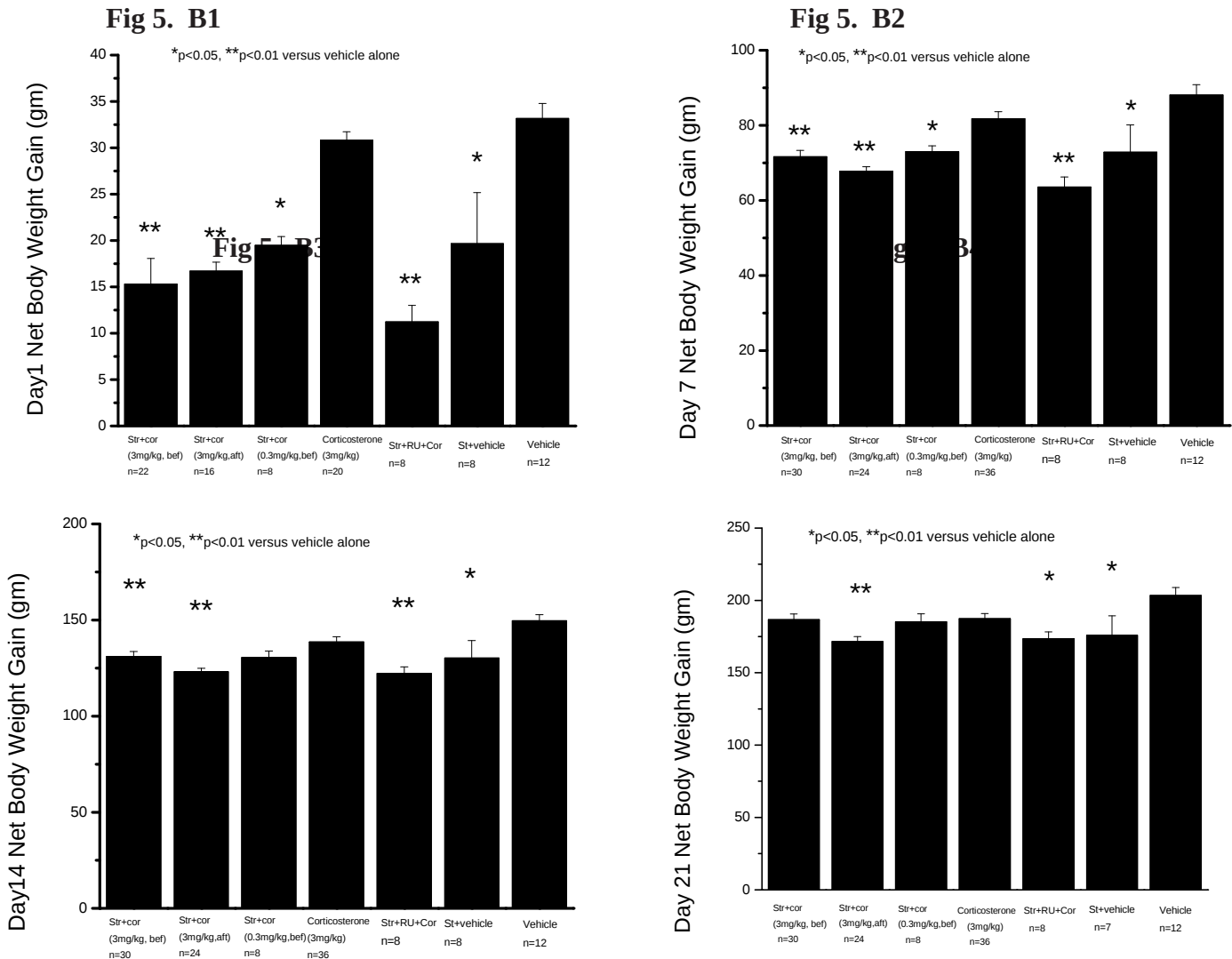


Figure 5B. The comparison of net body weight gains for groups of stress plus corticosterone (3mg/kg, 30 minutes before stress), stress plus corticosterone (3mg/kg, 30 minutes after stress), stress plus corticosterone (0.3mg/kg, 30 minutes before stress), corticosterone (3mg/kg), stress plus RU486 and corticosterone (3mg/kg, before stress), stress plus vehicle and vehicle alone 1 (B1), 7 (B2), 14 (B3) and 21 (B4) days following treatments. Asterisks (*) indicate significant differences between groups ($p < 0.05$) and (**) indicate $p < 0.01$.

Task 5: Pre-stress administration of the glucocorticoid receptor antagonist RU 486 with corticosterone to determine whether the antagonist can block the action of corticosterone as measured by ASR

The time, effort, materials, and 88 animals scheduled for the 1mg/Kg corticosterone trials above were devoted to establishing a procedure for delivering the corticosterone blocker RU486, together with the minimum effective dose of corticosterone, 3mg/Kg.. While the dose of RU486 alone proposed in the Plan, 50mg/Kg (Mondry, 2005) was tolerated by rats, when added together with the 3mg/Kg dose of corticosterone under conditions of stress, many of the rats died, probably because the adverse effect of RU486 as well as volume of ethanol vehicle required to dissolve and deliver those doses of RU486 and corticosterone is toxic under stressful conditions. (Since alcohol is toxic under stressful conditions, that many soldiers under battle conditions revert to alcohol does warrant a study in itself directed at counseling and treatment.)

We tried two approaches to circumvent the toxicity of the large volume of ethanol vehicle - reducing the dose of RU486, and eliminating ethanol altogether by replacing it with DMSO. Sixty four (64) animals were run using DMSO as the vehicle for dissolving RU486: 24 animals injected with corticosterone plus RU486 in DMSO, 8 animals injected with corticosterone plus RU486 in DMSO and stressed, and 32 controls injected with normal saline. Additionally, others animals were run with corticosterone in DMSO and stressed, with corticosterone in DMSO and not stressed, and with DMSO alone as a control. As with the ethanol vehicle, the animals became sick and many died, so DMSO as vehicle does not circumvent toxicity. Success was encountered when we continued to dissolve the RU 486 in a 20 % ethanol solution by warming up the solution to 60° C, but reduced the dose. Rats did tolerate a dose of 20mg/Kg RU486 in the presence of 3mg/Kg corticosterone and stress, and this dose was used in all of the data presented. We are anxious to have further support to run the full protocol accordingly. Running the full protocol would differentiate the positive effects of corticosterone from the deleterious effects of the ethanol vehicle used in all experiments to date. We are anxious to further explore the beneficial mechanisms of corticosterone and apply these to treatment of PTSD

Task 6: Determination of plasma corticosterone levels in frozen plasma samples from tail and trunk blood using a RIA kit and ICN protocol. We have analyzed an additional 118 frozen plasma samples using a DSL Rat Corticosterone EIA kit. We have found this method to be sensitive enough for our needs without generating radioactive waste that would result from using the RIA method originally proposed. Plasma samples are collected and frozen until there are enough samples to use up a whole kit.

Plasma corticosterone concentrations were elevated immediately after stress (716 ± 78 ng/ml in the stress group and 191 ± 29 ng/ml in the control group, $p < 0.01$). Twenty-one days after stress the differences between these two groups were not significant ($p > 0.05$) (Fig. 6). Twenty one days after stress the plasma concentrations did not show significant differences ($p > 0.05$) among the groups of stress plus vehicle, vehicle alone, stress plus corticosterone (3mg/kg) administered 30 minutes prior to stress, stress plus corticosterone (3mg/kg) administered 30 minutes after stress, stress plus corticosterone (0.3mg/kg) administered 30 minutes prior to stress, corticosterone (3mg/kg) alone, stress plus RU486 and corticosterone (3mg/kg) and the group of 0.9% sodium chloride injection alone (Table1).

Fig. 6. Plasma corticosterone concentrations of stress groups and control groups immediately

after stress and 21 days after stress.

Table 2 Plasma corticosterone concentration 21 days after treatments

	N	Mean (ng/ml)	Std. Error (ng/ml)
Treatment			
Stress + Vehicle	8	409.7088	43.89027
Vehicle	8	281.1537	34.27222
Stress+ corti (3mg/kg) prior to stress	16	401.2544	44.59017
Stress+ corti (3mg/kg) after stress	16	460.2500	47.26649
Stress+ corti (0.3mg/kg) prior to stress	8	595.0325	87.61129
Corticosterone (3mg/kg)	18	407.7150	78.71674
Stress + RU + corticosterone	8	499.1250	64.06817
0.9% NaCl	8	338.3438	85.52309

Task 7: Data analysis and preparation of manuscripts for publication

Data analysis is completed. Seven abstracts and posters detailing the experiments completed thus far in this project have been presented: at the 4th Annual Conference on the Neurobiology of the Amygdala and Stress, at USUHS on April 28, 2009 and April 21, 2010; at USUHS Research Week in May, 2009 and 2010; to the Military Health Research Forum held in Kansas City, MO August 31-September 3, 2009; to the Society for Neuroscience Annual Meeting on October 17, 2009 in Chicago, IL and on Nov. 16, 2010 in San Diego.

KEY RESEARCH ACCOMPLISHMENTS May 1, 2008 through Dec 6, 2010

- Corticosterone pretreatment (pre-stress) has a long term beneficial effect in reducing the enhanced fear response that results from exposure to the stress protocol.
- Corticosterone post-treatment (post-stress) has a mid-term beneficial effect in reducing the enhanced fear response that results from exposure to the stress protocol.
- Lower dose of corticosterone pretreatment (pre-stress) has no significant beneficial effect in reducing the enhanced fear response that results from exposure to the stress protocol.
- Administration of corticosterone reveals no effect on normalizing the hampered body weight gain 21 days after stress and is without effect on body weight gain immediately after the cessation of the stress protocol.
- Bolus administration of corticosterone has no significant impact on the basal fear response and body weight gain.
- Animals appear to have less tolerance for the glucocorticoid receptor antagonist RU 486. This is due to the large volume of ethanol vehicle required to deliver both the initially proposed dose of RU 486 and the corticosterone together. Our current recalculated dose of RU486 is efficacious as reported herein, and is applied for in proposed experiments.
- Plasma corticosterone levels are significantly lower in the controlled group as compared

to the stressed group at Day 0 and Day 21 after stress, consistent with that reported in the literature. In addition, corticosterone treatment has efficacy on ameliorating exaggerated fear response but has no efficacy in normalizing plasma corticosterone level and body weight gain in our animal model of PTSD.

REPORTABLE OUTCOMES

- Poster presentation at the Society for Neuroscience Annual Meeting, October 17, 2009 in Chicago, IL.
- Poster presentation at the Society for Neuroscience Annual Meeting, Nov. 16, 2010 in San Diego.
- Oral and poster presentation at the Military Health Research Forum, August 31-September 3, 2009 in Kansas City, MO.
- Poster presented at the 4th and 5th Annual conference on Neurobiology of Amygdala and Stress, April 28, 2009 and April 21, 2010, at the Uniformed Services University of the Health Sciences, Bethesda, MD.
- Poster presentation at Research Week, May 11-13, 2009, at the Uniformed Services University of the Health Sciences, Bethesda, MD.
- Poster presentation at Research Week, May 16-18, 2010, at the Uniformed Services University of the Health Sciences, Bethesda, MD.

CONCLUSION

Therapeutic administration of corticosterone appears to have beneficial effects on attenuating the delayed and exaggerated fear response in subjects who encounter traumatic stress. Thus, effective pharmacological intervention for PTSD requires protection of both the hormonal and the neuronal systems associated with the stress response from impairment that can initiate the pathophysiology of traumatic stress. At this time, we conclude: 1) Rats subjected to restraint/tail shock stress for three days developed an exaggerated and delayed acoustic startle response 14 days after stress. This was associated with cessation of body weight gain during the three day period of stress and body weight gain remained at reduced level in comparison with that of non-stressed control rats. 2) Administration of the glucocorticoid receptor agonist corticosterone (3 mg/kg) 30 minutes before stress attenuated the exaggerated acoustic startle response measured up to 21 days after stress but had no effect in ameliorating hampered body weight gain resulting from stress. 3) Administration of the glucocorticoid receptor agonist corticosterone (3 mg/kg) 30 minutes after stress attenuated the exaggerated acoustic startle response measured at 14 days after stress and did not ameliorate exaggerated fear response and retardation of body weight gain resulting after 21 days after stress. 4) Administration of the glucocorticoid receptor agonist corticosterone at lower concentration (0.3 mg/kg) 30 minutes before stress did not attenuate the exaggerated acoustic startle response to stress and has no significant impact on body weight gain resulting from stress. 5) The serum concentration of corticosterone is significantly higher in stressed rats than in non-stressed controls in 0 day and 21 days after stress. The corticosterone levels are significantly higher (716 ± 78 ng/ml and 596 ± 98 ng/ml) in the stressed group as compared to the non-stressed control group (191 ± 29 ng/ml and 374 ± 46 ng/kg) measured at Day 0 and Day 21 respectively after stress. The profile of plasma concentration of corticosterone further confirms that the data collected from the current animal model is consistent with that reported in the literature (Ottenweller et al., 1989; Servatius et al.,

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