Blunted Corticosterone Response to Acute Predator Stress Results in Long-Term Spatial Memory Impairment

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Abstract

Clinical research suggests that a blunted corticosteroid response to trauma may be associated with increased risk of developing post-traumatic stress disorder (PTSD). Therefore, we examined the influence of a blunted corticosterone response to stress on the development of PTSD-like behaviors, such as increased anxiety and impaired learning and memory, in rats. Male Sprague-Dawley rats were injected with metyrapone, an inhibitor of corticosterone synthesis, or vehicle prior to being exposed to an adult female cat for one hour. One week later, the rats were tested for anxiety-like behaviors (e.g., reduced open arm exploration, decreased locomotor activity) on an elevated plus maze and for spatial learning and memory in the radial-arm water maze. Analyses of post-stress serum samples verified that metyrapone blocked the stress-induced increase of corticosterone levels. Behaviorally, the blunted corticosterone response to stress had no effect on the development of anxiety-like behaviors. On the other hand, we found that metyrapone administration prior to stress significantly impaired long-term spatial memory. These findings suggest that reduced corticosteroid levels could interact with stress to produce deleterious effects on cognitive performance. Moreover, because anxiety-like behaviors were not intensified by the blunted corticosteroid response to stress, our findings also suggest that specific physiological responses to an acute trauma may intensify some, but not all, PTSD-like symptoms.

Keywords: Anxiety; Corticosterone; Memory; PTSD; Rat model; Stress

Introduction

Individuals who are exposed to life-threatening trauma are at significant risk of developing post-traumatic stress disorder (PTSD), which is characterized by intrusive memories, persistent anxiety, an exaggerated startle response and cognitive impairments [1-6]. Importantly, not every individual who is exposed to trauma develops PTSD [7], suggesting that those who do develop PTSD may retain some sort of predisposing genetic factors for PTSD or may respond to the traumatic event in a way that makes them more likely to develop the disorder. Indeed, research has suggested that an individual's hypothalamus-

pituitary-adrenal (HPA) axis response to a traumatic event could affect his or her likelihood of developing PTSD [8-10]. In these studies, researchers showed that individuals who developed PTSD exhibited significantly lower levels of cortisol after the traumatic event than those individuals who did not develop PTSD. Preclinical work has provided similar results by examining the development of PTSD-like behaviors in different strains of rats. For instance, Cohen and colleagues [11] reported that Lewis rats, which exhibit a significantly blunted corticosterone response to stress, are more prone to developing PTSD-like behaviors following an acute stressor than Fischer or Sprague-Dawley rats. However, the studies conducted on this topic thus far have not been able to determine whether it is the HPA axis response to an acute stressor that affects PTSD / PTSD-like behavior development or if reduced HPA axis activity is merely a baseline characteristic of the people / rats that are more likely to develop PTSD / PTSD-like behaviors.

Only one study of which we are aware has utilized an experimental inhibition of a rat's HPA axis response to stress in order to assess whether or not it would facilitate the development of PTSD-like behaviors. In that study, the investigators found that the combination of a blunted corticosterone and parasympathetic nervous system response to stress resulted in significantly greater anxiety on an elevated plus maze three weeks following a single stress exposure [12]. However, these results were observed when comparing the experimental groups to their respective controls only, and the effects of the manipulations on cognitive performance were not examined. This latter point is especially important because PTSD can be considered a disorder of memory, as individuals suffering from the disorder show marked impairments of learning and memory, a phenomenon that may be a result of intrusive memories transiently interfering with these individuals' ability to process new information [13-17]. Thus, the purpose of the present study was to determine whether or not a blunted HPA axis response to acute predator

stress would facilitate the development of PTSD-like symptoms, such as enhanced anxiety and impaired learning and memory, in rats. We predicted that stressed rats treated with a corticosteroid inhibitor would exhibit greater levels of anxiety and greater impairments of learning and memory than stressed rats treated with vehicle one week following stress exposure.

Materials and Methods

Animals

Male Sprague-Dawley rats (~150 g) that were bred at Ohio Northern University were housed on a 12h/12h light/dark schedule (lights on at 0700 hours) in Plexiglas cages (2 per cage) with free access to food and water. The Institutional Animal Care and Use Committee at Ohio Northern University approved all experimental procedures.

Pharmacological agents

Rats were injected intraperitoneally with metyrapone (150 mg/kg; N = 22) or vehicle (30% polyethylene glycol solution; N = 21) at a volume of 1 ml/kg. Metyrapone is a cytochrome P₄₅₀ inhibitor that prevents the conversion of deoxycorticosterone to corticosterone in the adrenal cortex [18].

Stress procedure

Thirty minutes following the injection, the rats were assigned to stress (metyrapone N = 11; vehicle N = 10) or no stress (metyrapone N = 11; vehicle N = 11) conditions. Rats in the stress condition were placed in a perforated wedge-shaped Plexiglas enclosure (Braintree Scientific; Braintree, MA; 20 x 20 x 8 cm), which was placed in a small room (2.41 x 1.5 x 2.26 m) with an adult female cat for 1 hr [19-22]. Rats in the no stress condition remained in their home cages for the same time frame.

Blood sampling

Following the stress / no stress manipulation, the saphenous vein of each rat was punctured with a sterile, 27-gauge syringe needle. A 0.2 cc sample of blood was collected from each rat within 2 min. The serum was subsequently assayed for corticosterone with an Enzyme ImmunoAssay kit from Enzo Life Sciences, Inc. (cat# 901-097; Ann Arbor, MI). All samples were diluted 1:50 and assayed per kit instructions.

Behavioral testing

Elevated plus maze: One week following the stress / no stress manipulation, the rats were placed on an elevated plus maze (EPM) for 5 min. The EPM is a routine assessment of anxiety [23] and consists of two open arms (11 x 50 cm) and two closed arms (11 x 50 cm) that intersect each other to form the shape of a plus sign. Rat behavior was videotaped by a JVC hard disk camera hanging above the EPM and scored offline by investigators who were blind to the experimental conditions of the animals. The investigators assessed the following measures: time spent in the open and closed arms, number of entries into the open and closed arms, number of rearing episodes and number of open arm head dips. Anxiety-like behavior is often evidenced by a reduction of open arm exploration (time spent in the arms and entries into the

arms), as well as a reduction of general behavioral activity (e.g., rearing) [24-25]. Open arm head dips, which are reflective of risk assessment behavior, are often reduced in stressed animals and can be another indicator of anxiety-like behavior. Closed arm time and entries are an indication of general locomotor activity, and in some cases, can be suppressed by stress as well.

Radial-Arm Water Maze: One day after EPM testing, rat spatial learning and memory was assessed in the radial-arm water maze (RAWM), a hippocampus-dependent task [19,20,22,26-28]. The RAWM consisted of a black, galvanized round tank (168 cm diameter, 56 cm height, 43 cm depth) filled with water (22°C). Six V-shaped stainless steel inserts (54 cm height, 56 cm length; 60-70° angle) were placed in the tank to produce six arms radiating from an open central area. A black, plastic platform (12 cm diameter) was placed 1 cm below the surface of the water at the end of one arm (referred to as the "goal arm"). The goal arm was different across rats to prevent the build-up of odor cues in any one arm. At the start of each trial, rats were released into one arm (referred to as the "start arm") facing the center of the maze and given 1 min to locate the platform. The start arm was pseudorandomly changed after each trial so that it was never the same for two consecutive trials. Several extra-maze cues (e.g., posters) were on the walls of the room to facilitate rat navigation in the maze. Once on the platform, rats were left undisturbed for 15 sec. If, during any trial, a rat did not locate the hidden platform within 1 min, it was gently guided to the platform by the experimenter. Spatial learning and memory was measured by counting the number of arm entry errors that rats made on each trial. An arm entry was operationally defined as a rat passing at least halfway down the arm; an arm entry error consisted of a rat entering on the of non-goal arms or, very rarely, a rat entering and exiting the goal arm without climbing onto the platform. The rats were given 12 acquisition trials to learn the location of the hidden platform, followed 60 min later by a single short-term memory trial. On the following day, the rats were given one more trial in the RAWM to assess their long-term memory for the platform location.

Statistical analyses

Prior to data analysis, normality tests were employed for all dependent measures. In cases where the distributions were not normal, non-parametric comparisons (independent samples Kruskal-Wallis tests) were utilized; this turned out to be the case for open arm head dips, short-term memory performance in the RAWM and long-term memory performance in the RAWM. However, we also show ANOVA results for these measures for the benefit of the reader. In cases where the distributions were normal, two-way ANOVAs were used to analyze the data; this turned out to be the case for all remaining data. For the two-way ANOVAs, stress (stress, no stress) and drug (metyrapone, vehicle) served as the between-subjects factors. A mixed-model ANOVA was used to analyze arm entry errors on the acquisition trials in the RAWM with stress and drug serving as the between-subjects factors and trial (trials 1-12) serving as the within-subjects factor. Several data from rats trained in the RAWM had to be excluded from the analyses, due to experimenter error. Outlier data points

that were more than 3 standard deviations beyond the exclusive mean were removed from all analyses. Alpha was set at 0.05 for all analyses.

Results

Physiological effects

Corticosterone levels: There were significant main effects of stress, $F(1,34) = 15.73$, and drug, $F(1,34) = 6.08$, and a significant Stress $\times$ Drug interaction, $F(1,34) = 19.20$ (p 's < 0.05). Stressed rats treated with vehicle exhibited significantly greater corticosterone levels than all other groups, indicating that metyrapone prevented the stress-induced increase in circulating corticosterone (see Figure 1).

Body weight: For body weight gained following stress exposure, there was a significant main effect of drug, $F(1,39) = 7.24$, $p < 0.05$, indicating that metyrapone-treated animals gained significantly less weight than vehicle-treated animals. However, there was no significant main effect of stress, $F(1,39) = 2.16$, and the Stress $\times$ Drug interaction was not significant, $F(1,39) = 0.70$ (p 's > 0.05).

Elevated plus maze

Open arm behavior: For the amount of time spent in the open arms (see Figure 2A) and the number of entries made into the open arms (see Figure 2B), there were no significant main effects of stress (time: $F(1,39) = 0.91$; entries: $F(1,38) = 0.29$) or drug (time: $F(1,39) = 0.23$; entries: $F(1,38) = 0.30$), and the Stress $\times$ Drug interactions were not significant (time: $F(1,39) = 1.22$; entries: $F(1,38) = 2.46$) (all p 's > 0.05). There was, however, a significant main effect of stress for open arm head dips, $F(1,38) = 6.58$, $p < 0.05$, indicating that the stressed rats made significantly fewer open arm head dips than the non-stressed rats (see Figure 2C). There was no significant main effect of drug on open arm head dips, $F(1,38) = 0.28$, and the Stress $\times$ Drug interaction was not significant, $F(1,38) = 3.04$ (p 's > 0.05). A non-parametric Kruskal-Wallis test confirmed the presence of a significant effect across groups for open arm head dips ($p = 0.01$).

Closed arm behavior: For the amount of time spent in the closed arms (see Figure 2D), there were no significant main effects of stress, $F(1,39) = 0.91$, or drug, $F(1,39) = 0.23$, and the Stress $\times$ Drug interaction was not significant, $F(1,39) = 1.22$ (p 's > 0.05). There was, however, a significant main effect of stress for closed arm entries, $F(1,38) = 9.02$, $p < 0.05$, indicating that the stressed rats made significantly less closed arm entries than the non-stressed rats (see Figure 2E). There was no significant main effect of drug for closed arm entries, $F(1,38) = 1.31$, and the Stress $\times$ Drug interaction was not significant, $F(1,38) = 1.00$ (p 's > 0.05).

Rearing: For rearing episodes on the EPM (see Figure 2E), there were no significant main effects of stress, $F(1,39) = 0.50$, or drug, $F(1,39) = 0.06$, and the Stress $\times$ Drug interaction was not significant, $F(1,39) = 0.01$ (p 's > 0.05).

Overall Movement (Open Arm Entries + Closed Arm Entries): The analysis of overall movement on the EPM revealed a significant main effect of stress, $F(1,38) = 4.27$, $p < 0.05$,

indicating that stressed rats made fewer arm entries, overall, than non-stressed rats. There was no significant main effect of drug, $F(1,38) = 0.96$, and the Stress $\times$ Drug interaction was not significant, $F(1,38) = 2.14$ (p 's > 0.05).

Radial-arm water maze

For the acquisition trials (see Figure 3A), there were significant main effects of trial, $F(11,330) = 17.08$, and drug, $F(1,30) = 7.61$, indicating that the rats made significantly fewer errors as the trials progressed and that rats treated with metyrapone made significantly fewer errors during acquisition than rats treated with vehicle (p 's < 0.01). There was no significant main effect of stress, $F(1,30) = 0.01$, and the Stress $\times$ Trial, $F(11,330) = 1.27$, Stress $\times$ Drug, $F(1,30) = 1.21$, Drug $\times$ Trial, $F(11,330) = 0.56$, and Stress $\times$ Drug $\times$ Trial, $F(11,330) = 1.53$, interactions were not significant (all p 's > 0.05).

For the short-term memory trial (see Figure 3A), there was no significant main effect of stress, $F(1,29) = 0.08$, or drug, $F(1,29) = 0.51$, and the Stress $\times$ Drug interaction was not significant, $F(1,29) = 0.70$ (p 's > 0.05). The lack of statistical significance for short-term memory was confirmed by a non-parametric Kruskal-Wallis test ($p = 0.81$).

For the long-term memory trial (see Figure 3B), the main effects of stress, $F(1,29) = 3.22$, and drug, $F(1,29) = 3.87$, as well as the Stress $\times$ Drug interaction, $F(1,29) = 3.28$, were all approaching significance (p 's < 0.08). A non-parametric Kruskal-Wallis test indicated the presence of a significant effect across groups for long-term memory performance ($p = 0.04$). Examination of the data suggested that these effects were being driven by the stressed rats injected with metyrapone committing more errors, an a priori hypothesis described above. Therefore, we conducted planned comparisons (corrected for multiple comparisons) between the stress-metyrapone group and all other groups on the long-term memory test trial. These comparisons indicated

Figure 2: The amount of time spent in the open arms (A), the number of open arm entries committed (B), the number of open arm head dips committed (C), the amount of time spent in the closed arms (D), the number of closed arm entries committed (E) and the number of rearing episodes committed (F) on the elevated plus maze one week following stress exposure. Stressed rats exhibited significantly fewer open arm head dips and closed arm entries than non-stressed rats. Data are presented as means $\pm$ SEM. ** $p < 0.05$ significant main effect relative to no stress.

that the stressed rats treated with metirapone made significantly more errors on the 24-hr memory test trial than all other groups (p 's < 0.05).

Correlational analyses

We conducted exploratory bivariate correlations between rats' corticosterone levels following stress and the behavioral measures collected one week later. When conducting such analyses for the entire sample, we observed negative relationships between corticosterone levels and open arm entries, $r(37) =$

-0.34 , closed arm entries, $r(37) = -0.35$, and open arm head dips, $r(37) = -0.48$ (p 's < 0.05). When these analyses were restricted solely to stressed animals, we observed negative relationships between corticosterone levels and open arm time, $r(18) = -0.52$, open arm entries, $r(18) = -0.58$, and arm entry errors committed on the long-term memory trial, $r(16) = -0.57$ (see Figure 4) (p 's < 0.05).

Discussion

Clinical work in humans has suggested that an individual's

acute physiological response to trauma may affect his or her likelihood of developing PTSD. One such finding has indicated that people who exhibit abnormally low cortisol responses to trauma are more likely to develop PTSD [8-10]. Since experimental work on this topic in humans is practically and ethically impossible, we conducted the present study to examine the effects of a blunted HPA axis response to stress on the development of PTSD-like behaviors in rats. As illustrated in Figure 2, we found that stress exposure, alone, led to less movement and fewer open arm head dips on the EPM, but that the expression of these behaviors was not exacerbated by reduced corticosterone levels during stress exposure. On the other hand, we found that a blunted HPA axis response to stress led to impaired long-term spatial memory in the RAWM (see Figure 3). Although these data are preliminary, they could suggest that reduced corticosterone levels at the time

of stress result in long-term cognitive impairments and that such an abnormal physiological response to trauma intensifies some, but not all, PTSD-like symptoms in rats.

We did not observe significant effects of stress on body weight gained or several behavioral measures on the EPM, including the most recognized measure of anxiety-like behavior, open arm time (see Figure 2A). We likely did not observe any differences in body weight because we employed a single stress exposure only. Chronic stress studies are more likely to reveal body weight changes in rodents and typically involve several weeks of stress. Nevertheless, we did find that even though the stressed rats spent a similar amount of time on the open arms as the non-stressed rats, they committed fewer open arm head dips (see Figure 2C), indicating a reduction of risk assessment behavior, potentially reflective of increased anxiety. Moreover, the stressed rats moved less in the closed arms (see Figure 2E), which is suggestive of a reduction of overall movement. This was corroborated by the detection of a significant main effect of stress in a subsequent analysis on overall movement (open + closed arm entries). We did not find an exacerbation of such effects as a result of a blunted HPA axis response to stress. If anything, exploratory correlational analyses revealed a negative relationship between corticosterone levels following stress exposure and open arms time, open arm entries, closed arm entries and open arm head dips, suggesting that rats exhibiting greater corticosterone levels following stress exhibited greater anxiety-like behavior on the EPM. This finding suggests that a blunted corticosterone response to stress could actually prevent anxiety-like behavior on the EPM, which is contrary to our hypotheses and contradicts the findings of Bui and colleagues [12]. Our findings may differ from those of Bui and colleagues [12] for a couple of reasons. First, we employed a higher dose of metyrapone in the present study (150 mg/kg) than that which

was employed by Bui and colleagues (75 mg/kg). Second, we tested the rats' behavior one week, as opposed to three weeks, following stress exposure. These methodological differences could explain the apparent discrepancy in findings and may also explain why we did not observe general stress effects on all measures of EPM behavior. That corticosterone levels following stress were positively associated with anxiety-like behaviors on the EPM could suggest that only certain PTSD-like symptoms in rats are exacerbated by a blunted corticosterone response to stress. Such a conclusion is consistent with previous work in rodents showing that pharmacologically blocking glucocorticoid receptors after stress exposure can prevent the development of anxiety-like behaviors on the EPM [24].

The most interesting, and novel, finding from the present study was that a blunted HPA axis response to stress resulted in a significant impairment of long-term spatial memory more than a week after stress exposure (see Figure 3B). Exploratory correlational analyses revealed a significant negative correlation between the post-stress corticosterone levels of stressed animals and the number of arm entry errors that they committed in the RAWM on the long-term memory test trial (see Figure 4). These findings cannot be attributed to a general impairment of learning as a result of the blunted HPA axis response to stress because the stressed rats treated with metyrapone exhibited performance during acquisition and the short-term memory trials that was statistically equivalent to all other groups. It is not exactly clear why a blunted HPA axis response to stress would exacerbate its effects on cognitive performance. Clinical research has shown that the administration of glucocorticoids can enhance learning and memory in people with PTSD, while impairing those processes in healthy controls [31-32]. In addition, several studies have reported that the administration of glucocorticoids either shortly after the trauma or after the development of PTSD can prevent / ameliorate the onset / maintenance of PTSD symptoms [33-37]. These findings suggest that the reduced HPA axis activity observed in people who are exposed to trauma or in those individuals who have PTSD could be directly related to PTSD symptom intensity. Thus, although the neurobiological mechanisms underlying the effects observed in the present study are not presently known, they do suggest that a reduced corticosteroid response to stress may intensify subsequent development of PTSD-like cognitive impairments.

The data presented in this manuscript should be interpreted cautiously. Metyrapone is a corticosteroid synthesis inhibitor, meaning that, in addition to reducing corticosterone levels, it likely led to an increase in the levels of corticotropin-releasing hormone and adrenocorticotrophic hormone by effectively removing the negative feedback that corticosterone exerts on glucocorticoid receptors. Therefore, it is possible that the presumed elevations of these hormones, which have been implicated in anxiety-like behavior themselves (38), could have influenced the observed effects. Future work will need to assess the levels of these hormones following a manipulation similar to the one reported here and/or examine the influence of such

substances on exacerbating PTSD-like behavior development following stress. In addition, determining baseline corticosterone levels before and/or after the stress / no stress manipulation would provide for a more comprehensive characterization of the role of the HPA axis in the *onset* of PTSD-like behaviors. This is important because even after development of the disorder, people with PTSD typically exhibit abnormally low baseline levels of cortisol, a finding that has been speculated to result from enhanced negative feedback of the HPA axis [39-41]. Thus, it is not known whether abnormally low cortisol levels are a predisposing, baseline characteristic that enhances these individuals' likelihood of developing PTSD following trauma or if such levels develop as a result of the disorder. Finally, in the present study, we studied male rats only. Although this has been a common bias in preclinical models of PTSD, future work needs to examine how female rats are influenced by similar manipulations, especially since extensive work in humans suggests that female are significantly more likely to develop PTSD than males [42].

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