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Research article

Cyclical corticosterone administration sensitizes depression-like behavior in rats

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HIGHLIGHTS

- Depression is characterized by repeated episodes over time.
- Most animal models focus on only one episode of depression.
- We subjected rats to two cycles of corticosterone treatment to mimic human depression.
- Our results suggested that depression-like behavior may sensitive over cycles.
- We also saw a decrease in behavioral recovery over cycles.

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ABSTRACT

Because stress is a significant risk factor for depression, many animal models of depression employ chronic stress as a precipitating event. However, almost without exception, stress-induced animal models of depression focus on a single bout of depression and therefore, they do not provide any means to understand the typical cycling of mood observed in most patients with depression. Here we assessed whether repeated cycles of exposure to the stress hormone corticosterone would sensitize depression-like behavior. Rats were treated with corticosterone (CORT; 20 or 40 mg/kg) or vehicle for two cycles (21 days each), followed by a 21-day recovery period. Depression-like behavior was assessed via repeated forced swim tests (FSTs) in the middle and at the end of each CORT treatment and at the end of each recovery period. Our results showed that CORT administration for two cycles produces increasingly greater effects on depression-like behavior and a decrease in recovery between cycles. Potential confounding effects of body weight and repetitive behavioral testing are considered in the interpretation of these effects. Our approach of using more than one cycle of CORT exposure provides strong face validity as it mimics several aspects of human depression. The use of multiple cycles of CORT exposure may provide a means to study the episode recurrence seen in more than 70% of patients with depression.

1. Introduction

Depression is a serious psychiatric disorder and a profound public health concern. The complex structure of human depression and the subjective nature of its symptoms have made the development of animal models extremely challenging.

Exposure to stress has a strong impact on the manifestation of depression. Clinical reports suggest that depressive episodes are often preceded by stressful or traumatic life events [1,2] and one of the key endocrine changes in depressed individuals is a dysregulation of the HPA axis [3], which can be normalized with antidepressant treatment [4]. Also, patients with Cushing's disease, a disorder characterized by chronically high levels of cortisol, show unusually high rates of depression [5]. Preclinical research reveals similar trends in that high levels of stress hormones are known to increase depression-like behaviors in rodents [6]. In addition, glucocorticoids have deleterious effects on neurochemistry and neuroanatomy and many of behavioral and neurobiological changes produced by repeated glucocorticoid administration are reversed by antidepressant treatment [6–9].

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Major depression is a highly recurrent disorder, and frequently characterized by repeated episodes over time. The available evidence suggests that 60% of individuals who have one depressive episode will have another, 70% of depressed individuals with two episodes will have a third, and 90% of depressed individuals with three episodes will have a fourth episode [10,11]. The probability of recurrence increases with the earlier age of onset of the initial episode, the severity of the episode, and with poor quality of recovery from the episode [11,12]. However, current animal models of depression do not provide a means to study the typical cycling of episodes across time because they generally focus on one cycle or exposure to chronic stress. Accordingly, in the current study, we aimed to recapitulate the cyclical disease course of depression and to test the hypothesis that depression-like behavior would be sensitized over two cycles of stress exposure. This question was addressed using a preclinical model of depression in which 21 daily injections of the stress hormone corticosterone (CORT) produces dose-dependent increases in depression-like behavior characterized by increased immobility in a forced swim test (FST), decreased sucrose preference, decreased sexual behavior, and impaired cognition [6,7,13–17,29]. We compared the effects of repeated and cyclic CORT treatment on forced swim test (FST) behavior in rats.

2. Materials and methods

2.1. Animals

Male Long-Evans rats (n = 30) weighing approximately 200–250 g were purchased from Charles River (Montreal, QC). The rats were individually housed in standard polypropylene cages with Purina rat chow and water available ad libitum. The colony room was maintained at a temperature of 21 °C with a 12 h:12 h light/dark cycle (lights on at 7:00 a.m.). All experimental procedures were conducted during the light phase of the light/dark cycle and in accordance with the Canadian Council on Animal Care and the University of Saskatchewan Committee on Animal Supply and Use (procotol #20050060).

2.2. CORT treatment

The rats were handled for seven days prior to any experimental manipulations. At the end of handling, the rats were weight matched and assigned to one of three different treatment groups: 20 mg/kg CORT (CORT 20 group: n = 10), 40 mg/kg CORT (CORT 40 group: n = 10), or vehicle (vehicle group: n = 10). Previous work has shown that both of these doses can increase depression-like behavior in rats, with the higher dose producing more robust effects [7,8,14–16]. CORT or vehicle was delivered once per day via subcutaneous injection between 09:00 and 11:00 h. CORT (Steraloids, Inc.) was suspended in 0.9 (w/v) physiological saline with 2% (v/v) polyoxyethylene glycol sorbitan monooleate (Tween-80, Sigma-Aldrich). Each cycle of injections comprised 21 consecutive days, followed by 21 days of injection-free recovery. The rats were left untouched in their home cages during recovery periods.

All rats were weighed on a daily basis and body weights were recorded for later analyses.

2.3. Behavioral testing

A modified one-day version of the FST was used to assess depression-like behavior, as described previously [13]. The FST was conducted in a rectangular Plexiglas swim tank (25 cm long × 25 cm wide × 60 cm high), filled with 27 ± 2 °C water to a depth of 30 cm. Each rat was placed individually into the swim tank for 10 min. Behavior in the swim tank was video recorded with a camera. After 10 min, the rat was removed from the tank, towel dried and placed back in its home cage to dry under a heat lamp for approximately 20 min. The time spent immobile, swimming, and climbing were scored as measures of depression-like behavior.

The rats were repeatedly tested during the course of the experiment. The FSTs were conducted in the middle (day 10) and at the end (day 22) of each cycle of CORT treatment, and at the end of each recovery period. FST procedures were conducted between 9 am and 5 pm, depending on the experimental time point (the middle or the end of the cycle). The experimental design is depicted in Fig. 1A.

2.4. Statistical analyses

The data were analyzed using the statistical package for social sciences (SPSS). Repeated measures analysis of variance (ANOVA) was used to measure overall main effects and interactions, with treatment as the between-subjects factor and time as the within-subjects factor. All repeated measures ANOVA analyses were tested for the sphericity assumption with Mauchly's test. The degrees of freedom were corrected using Greenhouse-Geisser sphericity estimates whenever the assumption was violated. In addition, separate one-way ANOVA's were used to compare the effect of treatment on dependent variables at each experimental time point, followed by Fisher's LSD post hoc tests when appropriate. The significance level was $p = 0.05$ for all statistical comparisons.

3. Results

3.1. Body weight

Fig. 1B shows the mean body weight for the rats in each group during the two cycles of CORT treatment. We found a significant main effect of time [$F(2, 50) = 350.7$, $p = 0.001$] and a significant treatment by time interaction [$F(4, 50) = 4.042$, $p = 0.007$], but no significant main effect of treatment ($p = 0.156$).

Group differences in body weight at each behavioral testing time point were investigated using planned comparisons with one-way ANOVAs. In the first cycle, the CORT rats gained significantly less weight than the vehicle rats. There was a significant main effect of group on day 10 [$F(2,27) = 5.405$, $p = 0.011$] and day 22 [$F(2,27) = 3.266$, $p = 0.05$]. Post hoc tests revealed that the CORT 40 rats weighed significantly less than the vehicle rats after ten days of injections ($p = 0.003$), and continued to do so until day 22 ($p = 0.018$). No significant group differences were detected after 21 days of recovery ($p = 0.941$).

In the second cycle, the CORT rats weighed less than the vehicle rats by day 10 but the difference between the groups missed statistical significance ($p = 0.098$). However, group differences in body weight were significant by day 22 [$F(2,27) = 4.845$, $p = 0.016$], and post hoc analyses revealed that the CORT 40 rats weighed less than the vehicle rats at this time ($p = 0.004$). No significant group differences were detected after 21 days of recovery ($p = 0.419$).

3.2. Forced swim test

3.2.1. Immobility

Fig. 2A–C shows the mean FST behavior displayed by the rats in all groups at all time points. With respect to immobility, we found a significant main effect of time [$F(4, 95) = 19.61$, $p = 0.001$], but no significant treatment by time interaction ($p = 0.09$). There was also a significant main effect of treatment [$F(2, 26) = 3.28$, $p = 0.05$] and post hoc analyses confirmed that the difference occurred between the CORT 40 rats and the vehicle rats ($p = 0.023$).

Analyses of group differences at each behavioral testing time point revealed that in the first cycle, CORT treatment had no significant effect on immobility on day 10 ($p = 0.187$). However, CORT