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Attenuation of social interaction-associated ultrasonic vocalizations and spatial working memory performance in rats exposed to chronic unpredictable stress

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HIGHLIGHTS

- CUS exposure did not alter sucrose preference in adult male Sprague Dawley rats.
- CUS exposure attenuated social interaction-associated ultrasonic vocalizations.
- CUS exposure attenuated cognitive performance on a spatial working memory task.
- CUS exposure resulted in attenuation of weight gain in CUS-treated rats.
- CUS exposure resulted in increased latency to feed in a novel environment.

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ABSTRACT

Exposure to unpredictable chronic mild stress (CUS) is a commonly used protocol in rats that is reported to evoke antidepressant-reversible behaviors such as loss of preference for a sweetened water solution which is taken as an analog of the anhedonia seen in major depression. However, the induction of anhedonic-like behavior by chronic mild stress, gauged by an animal's preference for sucrose solution, is not fully reproducible and consistent across laboratories. In this study, we compared a widely used behavioral marker of anhedonia — the sucrose preference test, with another phenotypic marker of emotional valence, social interaction-associated ultrasonic vocalizations as well as a marker of an anxiety-like phenotype, novelty-suppressed feeding, and cognitive performance in the eight arm radial maze task in adult male Sprague–Dawley rats. Chronic four-week exposure to unpredictable mild stressors resulted in 1) attenuation of social interaction-associated ultrasonic vocalizations 2) attenuation of spatial memory performance on the radial arm maze 3) attenuation of body weight gain and 4) increased latency to feed in a novelty-suppressed feeding task. However, chronic exposure to CUS did not result in any significant change in sucrose preference at one-week and three-week intervals. Our results argue for the utility of ultrasonic vocalizations in a social interaction context as a comparable alternative or adjunct to the sucrose preference test in determining the efficacy of CUS to generate an anhedonic-like phenotypic state.

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1. Introduction

It has been well established that chronic emotional stress plays a pivotal role in the genesis of many psychiatric disorders with induction of both short-lasting and long-lasting alterations in behavior and physiological functions [1,2]. Such emotional stressors are one of the main sources of stress in human life, especially for those low in the social hierarchy, and play a major role in the pathogenesis of anxiety and depressive disorders [3,4]. In social settings, stress can occur throughout the lifespan, and can range from childhood neglect to peer abuse such as school bullying in adolescence or workplace harassment in adulthood [5,6]. Furthermore, chronic stress may be associated with fearful (and life-threatening) events of traumatic nature such as violence, war, injury or assault [7].

There are very few animal models of human major depressive disorder (MDD) that can adequately provide the face, construct and predictive validity for bench research to be translated into bedside application. Mild Chronic Unpredictable Stress (CUS) is one such paradigm that has been used to model the human symptom of anhedonia (defined as loss of interest in daily activities that were previously

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enjoyable) [8]. While a sufficient volume of literature supports the efficacy of CUS in altering observable behaviors, sucrose testing is by far the most cited measure of 'anhedonia' [9]. The use of sucrose testing (of either consumption or preference) generalizes palatable taste reactivity as an index of hedonic state in laboratory rodents. However, reduction in preference for a sweetened water solution has been widely criticized as being unreliable due to variable responsiveness of rodents to CUS [10] and having possible relationships to body weight and nutritional status as well as caloric intake which may confound the results [11]. In fact, these observed effects may be limited to the gustatory circuitry and metabolic demand.

A large body of evidence has accumulated over the last two decades that highlights the difficulties associated with sucrose testing as a consistent measure of hedonic drive [12]. For example, chronic stress has no effect on sucrose consumption under a progressive ratio schedule as would be expected if hedonic drive were reduced [13]. Similarly, sucrose consumption was more dependent on food deprivation and weight changes seen with chronic stress paradigm, and independent of other elements of stress protocol [14]. While CUS reproduces characteristic behavioral responses, there is a need to validate objective alternatives to sucrose testing as a measure of a rodent's affective state. The goal of the present study was to compare the effects of CUS on sucrose preference to other behavioral markers relevant to major depressive disorder in order to increase the reproducibility of the paradigm.

Therefore, in Experiment A, we examined multiple measures to seek more reliable behavioral markers for the effects of CUS, starting with the sucrose preference test. Based on previously published studies, it was expected that the stressed rats would show a reduced preference for the sucrose solution [15]. However, given that sucrose preference has also been shown to paradoxically increase or remain unchanged with exposure to chronic stress, we also tested other behavioral markers of chronic stress in addition to sucrose preference test [16]. These markers included tests of body weight gain, separation/anticipatory ultrasonic vocalization and novelty-suppressed feeding. A total of 20 rats were used for this experiment (10 per treatment group).

Experiment A was followed by Experiment B with an additional test of a behavioral marker relevant to MDD, namely, spatial working memory in an 8-arm radial maze [17]. Spatial memory is a type of hippocampal-dependent learning and memory, and evidence suggests frequent impairment of hippocampal-dependent learning and memory in MDD [18]. A total of 30 rats were used for this experiment (14 control and 16 CUS). In total, 50 rats were used in Experiments A and B.

2. Materials and methods

2.1. Materials and methods — experiment A

The goal of the first experiment was to identify reliable behavioral markers for the effects of mild chronic unpredictable stress (CUS). The markers included assessment of gain in body weight, sucrose preference, novelty-suppressed feeding, and anticipatory ultrasonic vocalization after brief separation from cage-mate.

2.1.1. Animals and housing

For both Experiments A and B, adult male Sprague–Dawley rats (Charles River, Wilmington, Mass., USA) weighing 200–250 g at the start of experiment were housed two per cage (25 × 48 × 20 cm) in a temperature and humidity-controlled colony room (~21 °C, 40–50%) at the University of Mississippi Medical Center Laboratory Animal Facility. The rats were maintained on a reverse 12:12 light/dark cycle, with lights off at 0700 h. All behavioral testing took place during the dark phase of the cycle. Food and water were available ad libitum, except during testing. Before the beginning of experiments, all animals were handled for approximately 15 min, daily for 3 days. All procedures were approved by the University of Mississippi Medical Center Institutional Animal Care and Use Committee and conformed to the guidelines of the National Institutes of Health.

2.1.2. Sucrose preference

Prior to beginning of testing, rats were habituated to the presence of the two drinking bottles for 5 days (4 h each day) in their home cages. One of the bottles contained sucrose in increasing concentrations each day (0.1, 0.3, 1.0, 3.0, 10%). This allowed us to determine that a 3% sucrose solution consistently (S.E.M. < 10% of mean) elicited a 3-fold preference over tap water while the 1% solution did not reliably maintain a strong preference and the 10% solution elicited a larger, but much more variable preference (S.E.M. ~20% of the mean). Therefore, for all subsequent studies, we compared the preference for a 3% sucrose solution to tap water. Following this acclimation, rats had the free choice of either drinking the 3% sucrose solution or tap water for a period of 3 consecutive days (4 h each day). Sucrose preference was calculated as a percentage of the volume of sucrose intake over the total volume of fluid intake [11] and analyzed over the testing period of 3 days via two-factor ANOVA followed by planned comparisons using uncorrected univariate F-tests for between-cell comparisons.

There was a significant difference in sucrose preference between the three days [$F_{(2,38)} = 4.316$, $p < 0.05$]. Post hoc comparisons using the Tukey HSD test indicated that the mean (M) % preference score for the Day-1 sucrose preference ($M = 80.63$, $SD = 11.59$) was significantly different from the Day-2 sucrose preference (Mean = 71.99, SD = 7.84). However, the Day-3 sucrose preference (Mean = 76.74, SD = 11.64) did not significantly differ from either Day-1 or Day-2 sucrose preference. Since the sucrose preference differed significantly between the first and second day only, a two-day protocol of sucrose preference testing was employed during the CUS treatment.

2.1.3. Mild chronic unpredictable stress (CUS)

Rats were assigned to one of two groups ($n = 10$ each per group) and were either exposed to mild chronic unpredictable stress (CUS) or handled to serve as no stress controls. Rats in each group were matched as closely as possible for body weight, baseline sucrose preference and total fluid intake. Rats assigned to the CUS group were exposed to the CUS protocol shown in Table 1. This 10-day protocol was systematically repeated to maintain the element of unpredictability throughout the experiment and for a total of 35 days (5 weeks of CUS treatment). During this period, control animals were regularly handled, weighed and housed separately without any exposure to the CUS paradigm.

Body weight was measured before CUS (Day 0), 2 days after the beginning of CUS (Day 2) and every 4 days thereafter. Sucrose preference testing was conducted after 1 and 3 weeks exposure to CUS. USVs were

Table 1
CUS treatment paradigm — 2 stressors/day repeated daily: This 10-day protocol was systematically repeated to maintain the element of unpredictability throughout the experiment and for a total of 35 days (5 weeks of CUS treatment) for Experiment-A, and 28 days (4 weeks of CUS treatment) for Experiment-B. During both experiments, control animals were regularly handled, weighed and housed separately without any exposure to the CUS paradigm.

Day	Stressor 1	Stressor 2
Day 1	50 min cold room	60 min cage rotation
Day 2	4 h wet bedding	12 h lights on during dark cycle
Day 3	60 min restraint stress	3 h lights off during light cycle
Day 4	50 min cage rotation	15 h food and water deprivation during the dark cycle
Day 5	15 min cold room isolation	17 h isolation housing during light cycle in clean cage
Day 6	4 h wet bedding	3 h lights on during dark cycle
Day 7	30 min cage rotation	1 h lights on during dark cycle
Day 8	5 min swimming exposure during dark cycle	60 min restraint stress
Day 9	4 h wet bedding	12 h food deprivation during dark cycle
Day 10	45 min cold room isolation	6 h lights on during dark cycle

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