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Research report

Repeated social defeat stress enhances the anxiogenic effect of bright light on operant reward-seeking behavior in rats

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HIGHLIGHTS

- Anxiogenic bright light decreases lever-pressing for reward.
- Stress increases anxiety-like behavior.
- Stress increases the effect of anxiogenic light on lever-pressing for reward.

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ABSTRACT

Repeated stress can trigger episodes of depression, along with symptoms of anhedonia and anxiety. Although often modeled separately, anxiogenic factors potently modulate hedonic, or appetitive, behavior. While repeated stress can increase anxiety and decrease appetitive behavior, it is not clear whether repeated stress can influence the impact of anxiogenic factors on appetitive behavior. This study tests whether repeated stress shifts behavior in a task that measures anxiogenic-appetitive balance. To test this, adult male rats were trained to lever press for sucrose pellet reward, and the effect of anxiogenic bright light on this behavior was measured. The impact of the bright light anxiogenic stimulus on lever pressing was compared between groups exposed to either daily repeated social defeat stress or control handling. We found that repeated stress reduced exploration in the open field and decreased social interaction, but had minimal effect on baseline lever pressing for reward. Repeated stress substantially enhanced the effect of anxiogenic bright light on lever pressing. This effect was greater two days after the last stress exposure, and began to diminish within two weeks. These data demonstrate that the anxiogenic and anhedonic features induced by repeated stress can be separately measured, and that the impact of anxiogenic stimuli can be greatly enhanced after repeated stress, even in the face of appetitive drive. The data also demonstrate that some apparent anhedonic-like effects of repeated stress can be due to increased sensitivity to anxiogenic stimuli, and may reflect an imbalance in an appetitive approach-withdrawal continuum.

1. Introduction

Two major symptoms of depression are anhedonia and anxiety. These symptoms are sometimes viewed as two components of a tripartite model of depression [1] or expressions of abnormalities along an appetitive approach-withdrawal continuum [2] that has become unbalanced [3]. However, anhedonic and anxiety symptom expression is variable across patients with major depression. Understanding the balance between anxiogenic and appetitive stimuli, and their imbalance in depression, may provide hints about the source of symptom variability in patients, and ways to selectively target depressive symptoms. A balance between approach and withdrawal can be modeled in studies that pit anxiogenic stimuli against appetitive stimuli, and often demonstrate that anxiogenic stimuli can suppress appetitive behaviors. This is commonly observed in tests of novelty-suppressed feeding and drinking [4], conditioned suppression [5] and a range of conflict tests [6,7].

Repeated stress is a common trigger for depression. Repeated stress can induce symptoms of anxiety and anhedonia in humans

Abbreviations: ANOVA, analysis of variance; FR, fixed ratio; OF, open field; SI, social interaction.

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[8–12] and in rodent models [13–17]. Stress may cause an imbalance between the response to appetitive and anxiogenic stimuli that is similar to depression. While much is known about how anxiety influences appetitive behavior, little is known about whether stress shifts this balance. Previous studies demonstrate that stress further suppresses drinking in a punished drinking Vogel conflict test [18], and further suppresses feeding in a novel environment [19–21], consistent with a shift in favor of anxiety. However, in previous studies a confounding deprivation state is often imposed on the rat to induce consummatory behavior. In addition, both the appetitive and anxiogenic components are sensitive to stress in those tasks, making it difficult to parse the influence of stress on anxiety and appetitive drive. This study will test whether repeated stress shifts the balance towards anxiety-like behavior when appetitive and anxiogenic conditions are overlaid, using an operant appetitive task that is less sensitive to the effects of acute or repeated stress (lever-pressing for sucrose; [22–25]), and does not rely on induction of a deprivation state.

In these experiments, the effects of repeated social defeat on the balance between anxiety-like and appetitive behavior was measured. Bright light is an unconditioned anxiogenic stimulus [26–31] that can suppress appetitive behavior [32]. The interaction between anxiety and appetitive behavior was measured as the effects of bright light on conditioned operant lever pressing for a sucrose pellet. This was compared between adult rats that underwent repeated social defeat or control handling.

2. Materials and methods

All studies had prior approval of the Rosalind Franklin University Institutional Animal Care and Use Committee, and complied with the Guide for the Care and Use of Laboratory Animals (National Research Council, 2011). Care was taken to minimize animal distress and reduce the number of animals used.

2.1. Animals

Male Sprague-Dawley rats (Harlan Laboratories, Madison, Wisconsin) were used for these studies. Rats arrived at the Rosalind Franklin University vivarium at 53–58 days postnatal. The rats were provided water and food (Rodent Diet 2020X pelleted feed, Harlan Teklad) ad libitum. The housing rooms were set to a 12 h/12 h reverse light–dark cycle. Temperature was maintained between 64 and 79 F and the humidity was maintained between 30 and 70%. Rats were housed 2–3 per cage (polycarbonate solid bottom, 43.2 × 21.5 × 20.3 height, in cm), and were habituated to the facility for 1–2 weeks. Rats were handled daily for three days prior to initiation of training. All experiments were performed during the dark phase of the light–dark cycle.

2.2. Appetitive conditioning

2.2.1. Apparatus

Conditioning was performed in an operant chamber (Med Associates, ENV-001, St. Albans, VT). The chamber was enclosed within a sound-attenuating cabinet (Med Associates). Each cabinet was affixed with an IR-sensitive digital camera (Fire-i, Unibrain, San Ramon, CA), infrared lighting, and dim white house lighting (20 lx). There was a fan in each cabinet that provided airflow and ~60 dB of ambient noise. The chamber was also fitted with 2 levers, one designated as the active lever and the other designated as the inactive lever, a cue light placed proximal to the levers, and a food receptacle where sucrose pellets were delivered.

2.2.2. Appetitive conditioning procedure

Rats were taken from their home cages and individually transferred by transport cages to the procedure room, where rats were placed in the operant chamber. After each session, rats were returned to their home cage. Each rat was habituated to the operant chamber for 2 sessions (one/day) before training. During these 2 sessions, sucrose pellets (45 mg) were placed in both the food receptacle and on the active lever to facilitate subsequent learning. After two habituation sessions, appetitive conditioning sessions began. Each appetitive conditioning session was 30 min in length. Sucrose pellets were remotely delivered when the rat neared the active lever, in order to facilitate differentiation between the active and inactive lever. When the rat pressed the active lever, the cue light (green, 2.5 cm diameter, 1 s) was triggered immediately and a sucrose pellet was delivered 1 second after the cue light (Fixed ratio schedule (FR) 1). Manual delivery of pellets ceased by the third training session, as rats displayed preference for the active levers by this session. By the fourth day of training, and throughout the remainder of the entire experiment, rats consumed all delivered pellets. The number of presses on active and inactive levers was recorded for each session. All rats were required to meet a minimum criterion of 35 active lever presses by their final session in order to move onto the next phase of the experiment. This criterion was attained between 7 and 9 days. One day after criteria was reached, rats were tested at a FR 4 schedule for 30 min.

2.3. Treatment groups: social defeat and control

There were two treatment groups: social defeat stress and control. These groups were further divided into two subgroups: rats tested after 2 days ($n = 8$ rats/group, and a second cohort of $n = 8$ rats/group for experiments with no anxiogenic light; see below, Section 2.6) and rats tested after 2 weeks (14–17 days; $n = 14$ rats/group) for a total of 60 rats. This does not include 3 rats that were excluded because they did not reach lever pressing criteria. The number of rats was based on the expected effect size from other studies. Rats were matched for number of lever presses on the day that criteria was reached, and then randomly assigned into control or social defeat treatment group. Beginning one day after rats were tested at the FR 4 schedule, the rats were exposed to social defeat or control handling once/day for 5 consecutive days (Fig. 1A). Social defeat began by transporting rats to a procedure room, and placing an "intruder" (male Sprague-Dawley rat) into the home cage of a "resident" (male retired breeder Long Evans rat, Harlan Laboratories). The two rats were allowed to be in physical contact with each other for a maximum period of 15 min. They were separated when one of the following conditions was met: submission of the intruder, 15 min with no submission, 10 attacks with no submission, 5 min without any attack, or any attack that wounded a rat. The intruder rat was separated using a wire mesh cage placed over the animal and it remained in the residents' cage for an additional 15 min to permit unrestricted visual, auditory, and olfactory contact without any further physical attacks. Intruder rats were rotated through different resident rats each day. Control handling comprised of placement of rats into a transport cage for 20 min. At the end of each session, rats were returned to their home cage. Experimental rats remained in their home cage for 2 days or 14–17 days before subsequent behavioral testing. After this interval, rats were tested in the open field, social interaction, operant lever pressing for sucrose pellets, and suppression of sucrose seeking by anxiogenic stimulus (Fig. 1A). Over the course of these experiments, rats were weighed daily and their body condition was assessed.

2.4. Open field

Rats were individually placed in an open field (61 cm × 89 cm) in a room with dim white light (20–25 lx; 5 min) and dim red light.