Behavioural Brain Research 256 (2013) 305–310

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Chronic psychosocial stress makes rats more 'pessimistic' in the ambiguous-cue interpretation paradigm

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HIGHLIGHTS

- We investigated whether negative judgement bias in rats can be induced psychosocially.
- Rats were subjected to chronic social defeat in the resident–intruder paradigm.
- Cognitive judgement bias was measured in the ambiguous-cue interpretation tests.
- Rats subjected to chronic psychosocial stress are 'pessimistic'.

ARTICLE INFO

Article history:
Received 29 July 2013
Received in revised form 22 August 2013
Accepted 24 August 2013
Available online 28 August 2013

Keywords:
Stress
Ambiguous cue
Pessimism
Rat
Depression
Social Defeat

ABSTRACT

Human decisions are often biased by emotions. Stressed and depressed individuals tend to make negative, pessimistic judgements while those in positive affective states are often more optimistic. Chronic psychosocial stress has previously been shown to induce a spectrum of behavioural and physiological changes in rats that are considered the correlates of depressive symptoms in humans. In this study, we investigate whether chronic social defeat makes animals more 'pessimistic'. To measure the changes in cognitive judgement bias, we applied the ambiguous-cue interpretation paradigm. In the operant boxes, the rats were trained to press one lever in response to one tone to receive a reward and to press another lever in response to a different tone to avoid punishment. Cognitive bias was tested by measuring the pattern of animals' responses to a tone of intermediate frequency (ambiguous-cue). To induce chronic psychosocial stress, we subjected the animals to daily social defeat in the resident–intruder paradigm for 3 weeks. We report that chronic psychosocial stress makes rats more pessimistic.

1. Introduction

Stress, especially chronic stress, is one of the most important contributing factors to depression in humans [1,2]. The impact of stress on the development of mood disorders has been investigated thoroughly in preclinical animal studies for over 30 years. A great variety of stressors are used in these studies; however, very few of them are relevant to the stressful situations experienced by humans. Chronic psychosocial stress based on repeated social defeat is one of the most naturalistic and relevant rodent models of chronic stress and depressive symptoms [3,4]. In this paradigm, an adult male (the intruder) is introduced into the home cage of an unfamiliar, aggressive individual (the resident). The animals interact rapidly, fight and the intruder usually loses the encounter (social defeat). The experimenter terminates the interaction as soon as the intruder shows signs of submissive behaviour, which minimises injury while emphasising the psychosocial component of the stress [5]. A number of studies show that chronic exposure to social defeat produces a variety of changes that can be considered physiological and behavioural correlates of depressive symptoms in humans. These include reduced preference to sucrose solution (anhedonia), increased immobility time in the forced swim test (motivational deficits), reduced locomotor and exploratory activity and hyperactivity of the hypothalamic pituitary adrenal (HPA) axis [3]. The majority of these changes are selectively reversible by antidepressant treatments [6–8]. However, surprisingly little is known about the cognitive effects of chronic social stress in rodents. Using the contextual and cued fear-conditioning tests, several studies report socially induced impairments in working memory and enhanced fear memory [9,10]. Nevertheless, it

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http://dx.doi.org/10.1016/j.bbr.2013.08.036

remains unknown whether chronic loss of social status can induce other cognitive impairments in rodents.

In humans, stressed and depressed individuals tend to expect bad things to happen – they see the glass as half empty rather than half full [11–13]. The same is true for animals. In a seminal study by Harding et al. [14], rats showed negative cognitive judgement bias when they were subjected to chronic mild stress, another preclinical model of depression. In another landmark study, Enkel et al. [15] reported the presence of negative processing bias in congenitally helpless rats, a genetic animal model of depression. Moreover, mimicking the stress-related changes in endogenous neuromodulation using a combined noradrenergic-glucocorticoid challenge also made rats more 'pessimistic' [15].

We trained rats in operant Skinner boxes to press one lever in response to one tone to receive a food reward and to press another lever in response to a different tone to avoid punishment by electric foot shock. After attaining a stable level of discrimination performance, the animals were tested for their responses to a tone of intermediate frequency, and the pattern of their responses to this ambiguous cue was taken as an indicator of the animals' baseline cognitive bias. Subsequently the rats were subjected either to daily social defeat in the resident–intruder paradigm for a period of 3 weeks (stressed group) or daily handling (control group) and re-tested in the ambiguous cue interpretation tests [15–17].

2. Material and methods

2.1. Ethics statement

Experiments were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals and approved by the Ethics Committee for Animal Experiments at the Institute of Pharmacology at the Polish Academy of Sciences.

2.2. Subjects and housing

Forty male *Sprague Dawley* rats (Charles River, Germany) weighing between 175 g and 200 g upon arrival were used in this study. The rats were group-housed (four rats/cage) in a temperature-controlled room (21 ± 1 °C) with 40–50% humidity under a 12/12 h light/dark cycle (lights on at 06:00 h). For all of the experiments, the rats were mildly food restricted to approximately 85% of their normal food intake. This was achieved by providing 15–20 g of food per rat per day (standard laboratory chow). The food restriction started 1 week prior to training. Water was freely available, except during the test sessions. The behavioural procedures and testing were performed during the light phase of the light/dark cycle.

Male *Wistar* rats (Charles River, Germany) weighing 450–500 g were used as residents. These animals were housed in pairs with age-matched sterilised females (Charles River, Germany) in a separate room. Housing conditions were the same as for the *Sprague Dawley* rats.

2.3. Apparatus

The behavioural tasks were performed in eight computer-controlled Skinner boxes (Med Associates, St Albans, Vermont, USA) located in the room adjacent to housing facility. Each box was equipped with a light, speaker, liquid dispenser (set to deliver 0.1 ml of 5% sucrose solution), two retractable levers, and a grid floor through which scrambled electric shocks (0.5 mA) could be delivered. The levers were located at opposite sides of the feeder. All of the behavioural protocols, including the data acquisition and recordings, were programmed in Med State notation code (Med Associates). The experimental procedures for the ambiguous-cue interpretation (ACI) test used in this study were modified versions of the procedures previously described by Enkel et al. [15] and have been described elsewhere [16,17].

2.4. Behavioural training

2.4.1. Positive tone training

During this phase, rats were trained to press the lever located on the left side of the feeder to receive the sucrose solution when a tone [50 s, 2000 Hz at 75 dB sound pressure level (SPL) or 9000 Hz at 75 dB SPL (counterbalanced)] signalled reward availability. Due to its association with a palatable reward, this tone acquired a positive valence and was referred to as the "positive tone", and the associated lever was referred to as the "positive lever". A reliable active lever pressing for the reward was achieved in three training steps: (a) presentation of the positive tone (lasting 50 s) co-occurred with a constant delivery of the sucrose solution, and this was followed by a 10 s inter-trial interval (ITI); (b) presentation of the positive tone co-occurred with a left lever extension and was followed by a 10 s ITI (each lever press during the tone was continuously rewarded by sucrose solution delivery); (c) procedure as in (b) with the exception that after the first lever press and reward delivery, the tone was terminated and followed by a 10 s ITI. During the ITIs the levers retracted. Each training session lasted for 30 min, and the training sessions continued until the animals attained a stable performance on each of the training steps (more than 200 responses maintained over three consecutive training sessions during step (b); a minimum of 90% successful responses to the positive lever following positive tone presentation maintained over three consecutive sessions during step (c). Positive tone training was followed by negative tone training.

2.4.2. Negative tone training

During this stage, the rats were trained to press the lever located on the right side of the feeder to avoid an electric shock [0.5 mA, 10 s) when another tone (9000 Hz at 75 dB SPL or 2000 Hz at 75 dB SPL (counterbalanced)] signalled a forthcoming punishment. Due to its association with a concomitant punishment, this tone acquired a negative valence and was referred to as the "negative tone". The associated lever was referred to as the "negative lever". A reliable active lever press avoidance response was achieved in two training steps: (a) the presentation of the negative tone was accompanied by the occurrence of electric shocks unless the rat pressed the right (negative) lever, which terminated the shock and tone presentation; (b) the presentation of the negative tone preceded the occurrence of the electric shocks. The delay from the tone onset to the electric shock occurrence was progressively increased from 1 s to 40 s. Pressing the negative lever before the shock onset terminated the tone and began a 10 s ITI, designated the "prevention response". Pressing the negative lever after the shock onset terminated the tone and shock and was referred to as the "escape response". The maximum duration of the tone/shock application was 50 s (i.e., 40 s of tone presentation followed by 10 s of a tone/shock co-occurrence), and the tone presentations were separated by 10 s ITIs. During the ITIs the levers retracted. Daily training sessions consisted of 40 tone presentations. The animals had to accomplish at least 60% correct prevention responses maintained over three consecutive training sessions before proceeding to the discrimination training.

2.4.3. Discrimination training

During this phase, the rats were trained to discriminate between positive and negative tones by responding to the appropriate levers (as learned in previous training stages) to maximise reward and minimise punishment delivery. The tones, which consisted of 20 positive and 20 negative tones, were presented pseudo-randomly and separated by 10 s ITIs during which the levers retracted.