



Research report

Early fear as a predictor of avoidance in a rat model of post-traumatic stress disorder

Xiaoyu Chen^a, Yonghui Li^b, Sa Li^a, Gilbert J. Kirouac^{c,*}^a Department of Oral Biology, Faculty of Dentistry, University of Manitoba, Winnipeg, Manitoba, Canada^b Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, China^c Departments of Oral Biology and Psychiatry, Faculties of Dentistry and Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

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ABSTRACT

Exposure of humans and animals to an intensely fearful experience can lead to an enduring behavioral profile involving fear and avoidance. The present study examined if rats that show more fear to a novel tone one day after exposure to footshocks exhibit more avoidance-like responses over a 4-week period. Rats were exposed to an episode of moderately intense footshock (5×2 s episodes of 1.5 mA presented randomly over 3 min). Shock rats that exhibited a high level of fear (HR) to a novel tone one day after the shock exposure showed more avoidance of open spaces and novel rats when compared to shock rats that exhibited a lower level of fear to the novel tone (LR). Similarly, HR emitted more ultrasonic vocalization in the dysphoric range (20–30 kHz) when placed in a novel chamber or the chamber in which shock was given. This study highlights the importance of early fear as a contributing factor for the development of lasting changes in avoidance. These results also support the view that the presence of an intense peritraumatic stress response may be a predictor of the subsequent development of a lasting negative emotional state in humans exposed to trauma.

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1. Introduction

Individuals exposed to an event involving intense fear, helplessness or horror normally develop a number of psychological and physiological responses that can vary in terms of intensity and duration. A typical acute reaction to such an event involves a combination of symptoms involving re-experiencing of the event in the form of memories and flashbacks combined with hyperarousal and feelings of dissociation [1,2]. For most people, the emotional reaction to a traumatizing event will dissipate over days or weeks [3–5], but in some individuals, the reaction does not normalize and can lead to psychological distress and the diagnosis of post-traumatic stress disorder (PTSD) [3–5]. As such, PTSD can be considered a disorder of recovery since it results from a failure to recover from a normal negative emotional reaction to a traumatic event [6,7]. The fact that the majority of traumatized individuals do not go on to develop PTSD underscores the importance of individual differences in responding and recovery from a life threatening experience [6,8].

Clinical evidence also indicates that many individuals exposed to severe trauma subsequently exhibit fear-like reactions when

confronted with reminders of the trauma or when faced with mildly stressful situations not directly related to the trauma experience [3,9]. Similar to the effects of trauma in humans, rodents exposed to intense fear-inducing situations can develop fear responses to situations which are not directly related to the trauma experience [10]. For example, rodents exposed to footshocks not only show a strong fear response when re-exposed to the shock apparatus or discriminative cues associated with the shocks, but also display a fear-like response when exposed to novel chambers or sounds [11–16]. Rodents pre-exposed to shock also exhibit a decrease in social interaction with other rodents and avoidance of areas of mazes involving some level of novelty or unknown risk [12,14,15,17–19], providing further evidence that fear can generalize to a variety of situations. It is also apparent from a number of studies that the development of fear responses in pre-shocked rodents is dependent on the intensity of the shock exposure [12,20–22] and that individual differences in fear generalization can account for some of the variability in the fear learning that can occur after the shock exposure [20].

While it has been difficult to establish a causal link between the early effect of trauma (peritraumatic period) and the subsequent development of PTSD in humans [1,2], it is possible that differences in how individuals respond immediately after trauma may contribute to whether PTSD develops [23]. Part of the difficulty in providing clinical evidence for such a link may be due to heterogeneity in the trauma population as well as the intensity and types of their trauma experienced in subjects studied. The present study

* Corresponding author at: Department of Oral Biology, Faculty of Dentistry, 780 Bannatyne Avenue, Winnipeg, Manitoba R3E 0W2, Canada. Tel.: +1 204 977 5696, fax: +1 204 789 3913.

E-mail address: kirouac@cc.umanitoba.ca (G.J. Kirouac).

Table 1
Timeline of the behavioral tests.

Day 1	Shock exposure
Day 2	Small open field test
Day 10	Social approach and avoidance test
Day 11	Novel plastic box test
Day 12	Shock chamber exposure
Day 25	Social approach and avoidance test
Day 26	Big open field test
Day 27	Shock chamber exposure
Day 31	Defensive withdrawal test

takes the advantages provided by a rat model of PTSD to determine if the intensity of early generalized fear response is related to the long-term expression of avoidance-like behaviors. The study also highlights the importance of individual differences in the reaction to fear and trauma to further help validate the footshock model.

2. Materials and methods

2.1. Animals and housing

Subjects were adult male Sprague-Dawley rats ($n = 46$) weighing 130 ± 10 g upon arrival. They were pair-housed in the plastic cages in a colony room on a 12 h/12 h light/dark cycle (lights on 06:00 h) with controlled temperature ($20\text{--}24^\circ\text{C}$) and humidity (40–70%). Animal had free access to food and water in their home cages. All of the experimental procedures were in compliance with the Canadian Council on Animal Care and approved by Research Ethics Review Board of University of Manitoba.

2.2. Handling and testing

Animals were handled for 5 min on alternate days during a 10-day adaption period. All the shock procedure and behavioral tests were done in the light cycle of the day (09:00–17:00 h) in a test room which was different from the colony room. All the behavioral tests were videotaped and later scored by three experimenters blind to the conditions. The reliability score between raters ranged between 0.94 and 0.97 (correlation coefficient) and the data from two observers were averaged for statistical analysis.

2.3. Footshock procedure

The timeline of the footshock exposure and the behavioral tests is shown on Table 1. On Day 1, rats were transferred to the test room with bright light (400–500 lx) and placed into an inescapable shock chamber with a grid floor (MED Associates, St. Albans, VT, USA). The shock chamber is composed of two walls of clear Plexiglas and two opaque gray walls. After a 2 min acclimation period, rats were exposed to footshocks (5×2 s of 1.5 mA with an intershock period of 10–50 s presented randomly over 3 min) which was given by a commercially available scrambler (MED Associates). The rats were kept in the chamber for another 60 s before they were returned to their home cages. Nonschok rats spent the same amount of time in the chamber but no shocks were delivered. The shock chamber was cleaned with ethanol (10.0%) and the bedding under the grid floor was changed for each animal.

2.4. Behavioral tests

2.4.1. Acute fear response to novel environment

Acute post-shock fear sensitization was assessed on Day 2 by measuring the amount of freezing expressed in rats placed in a novel chamber (made of black Plexiglas and measuring length 65 cm $\times$ width 40 cm $\times$ height 50 cm) with a light intensity of 3–5 lx. The duration of the test was 6 min which was composed of a 3 min period with background noise and the second 3 min period with a novel auditory tone present (9 kHz, 75 dB against background noise levels of 45–50 dB). The percentage of freezing (the freezing duration/total exposure time) was scored for both sessions. Freezing was defined as the completely lack of body movement except breathing movements as previously described [24]. The novel test chamber, as well as other test chambers, was cleaned with ethanol (10.0%) after each test subject.

2.4.2. Fear response to novel and shock chambers

The fear response to novelty was assessed on Days 11 and 26 after the shock. On Day 11, rats were placed in a novel clear plastic chamber (length 22 cm $\times$ width 28 cm $\times$ height 35 cm) for 3 min. On Day 26, rats were placed in the center of a large open field (length 80 cm $\times$ width 80 cm $\times$ height 40 cm) for 5 min. Both chambers were illuminated with a light of 8–10 lx. The percentage of freezing was calculated in both novel environments. In addition, ultrasonic vocalizations (USV) emitted during the novel chamber exposure on Day 11 were recorded using a specialized detector

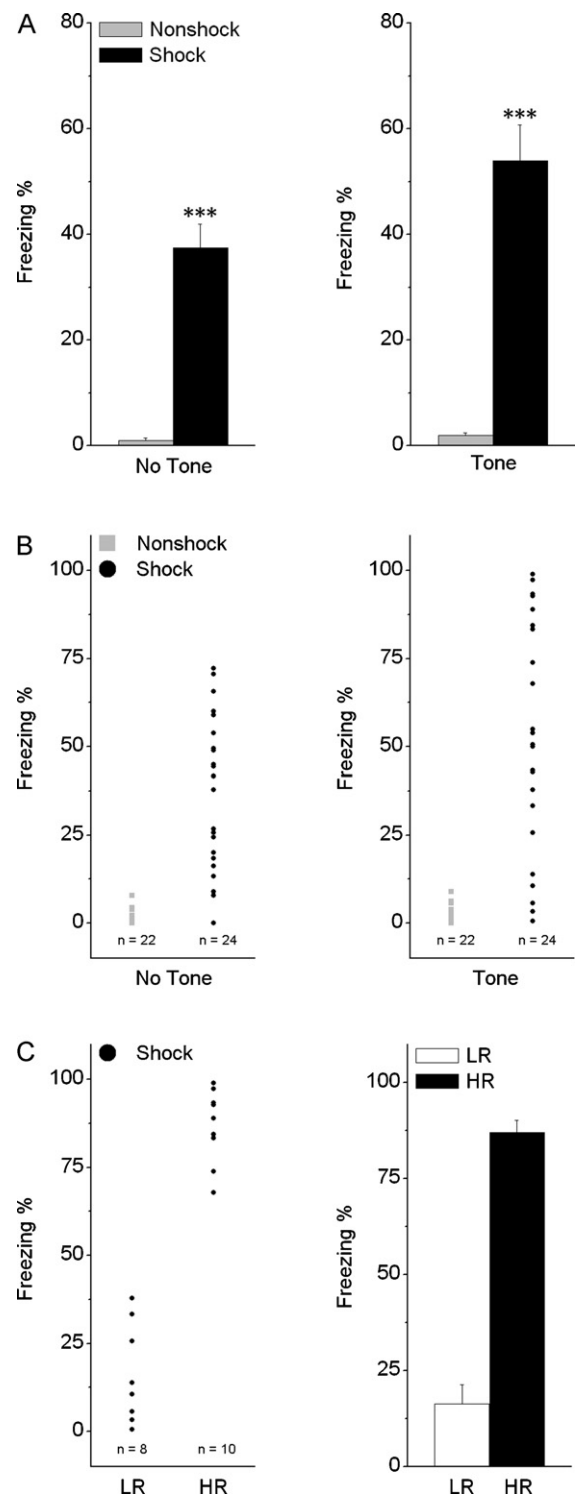


Fig. 1. Freezing response to a novel small open field and tone 24 h after footshock exposure in nonschok and shock rats (A). Shock rats displayed a wide range of freezing responses as shown in plots of individual freezing responses to the small open field before and after the presence of a novel tone (B). Shock rats were subdivided into low responders (LR) and high responders (HR) based on their freezing responses to the novel tone (C). The values in the histograms are mean $\pm$ SEM. *** $p < 0.001$.

(Med Associates) and the recording was later analyzed for the presence of calls within the dysphoric range (20–30 kHz). The contextual fear response was measured on Days 9 and 27 by placing the rats in the same shock context for 5 min (no shock delivered). The percentage of freezing and the number of USV emitted in the shock chamber were recorded and analyzed as described above.

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