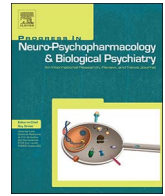




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Behavioral effects of early life maternal trauma witness in rats



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ABSTRACT

Background: Earlier, we have reported that post-traumatic stress disorder (PTSD)-like behaviors developed in rats that witnessed their cage mates undergo repeated traumatic stress. More recently, we published that early life physical traumatic stress leads to later life depression-like behaviors in rats. Whether early life trauma witness causes later life PTSD-like behaviors is not known. Also unclear are sex-specific stress-induced behavioral variations in later life. The early life witness component of stress is an important aspect of stress-induced psychopathologies and must be investigated.

Objective: Here, we have examined the impact of early life repeated witnessing of traumatic events by pups from post-natal day (PND) 21–PND27, on later life behaviors at PND60, and the behavioral impact of postpartum traumatic stress in female rats.

Methods: We used a modified version of rodent social defeat model to induce postpartum stress in female rats and trauma witness stress in pups. One female Sprague-Dawley rat (intruder) was introduced into the cage of an aggressive Long-Evans male rat (resident). The encounter between the two resulted in attacks between the female rat and the Long-Evans male rat. Three exposures of social defeat (attacks) were given for 7 consecutive days. The social defeat traumatic events were witnessed by 6 pups (offspring of the intruder female rat, PND21–27), placed in six separate enclosures surrounding the cage. The objective of this experiment was three-fold: 1) to test later life behavioral effects in pups from witnessing maternal defeat, 2) to examine gender susceptibility of pups in maternal defeat witness-induced behaviors, 3) to test behavioral effect in female rats 24 h after receiving the last social defeat exposure.

Results: We observed that while anxiety-like behavior assessed in open-field and elevated plus-maze tests, was not affected in male or female rats upon witnessing repeated maternal traumatic stress, depression-like behavior in forced-swim test was observed at PND60 in both male and female rats, with greater effect in male rats. No change was observed in learning and memory functions using radial arm water maze test in both male and female rats. Interestingly, socially defeated female rats (dams: mother of the pups) developed both anxiety and depression-like behavior with no change in learning-memory function when compared to control female rats.

Conclusions: Our findings suggest that early life maternal stress witness history leads to depression-like behavior in both male and female adult rats, and dams developed both anxiety and depression-like behaviors.

1. Introduction

According to American Psychological Association, ~15.5 million children in the United States witness physical or emotional abuse of a parent, most commonly that of their mother (McDonald et al., 2006). Clearly, children raised in abusive households who witness parental abuse carry the psychological burden of helplessness, which often expresses in the form of conduct disorders or behavioral deficits (Stirling et al., 2008). Additionally, parental violence causes post-natal depression (Seng et al., 2013), which can impair childcare ability of the mother, increasing the likelihood of child abuse and neglect. Taken together, the effects of maternal abuse are damaging not only for the

mother but also for the children. While examining the link between maternal abuse and mental well being of the children as well as that of the mother are important to help devise appropriate behavioral and therapeutic interventions, conducting these studies in children with abuse or trauma history or in abused women, are difficult to carry out. Therefore, animal models are valuable in studying the behavioral consequences and the biological imprinting of trauma. Although animal models cannot accurately reveal the impact of traumatic events but are excellent tools that can provide useful insights and guide both therapeutic and management interventional strategies.

Recently, we reported that rats witnessing traumatic events (social defeat of a cage-mate) exhibited severe behavioral deficits resembling

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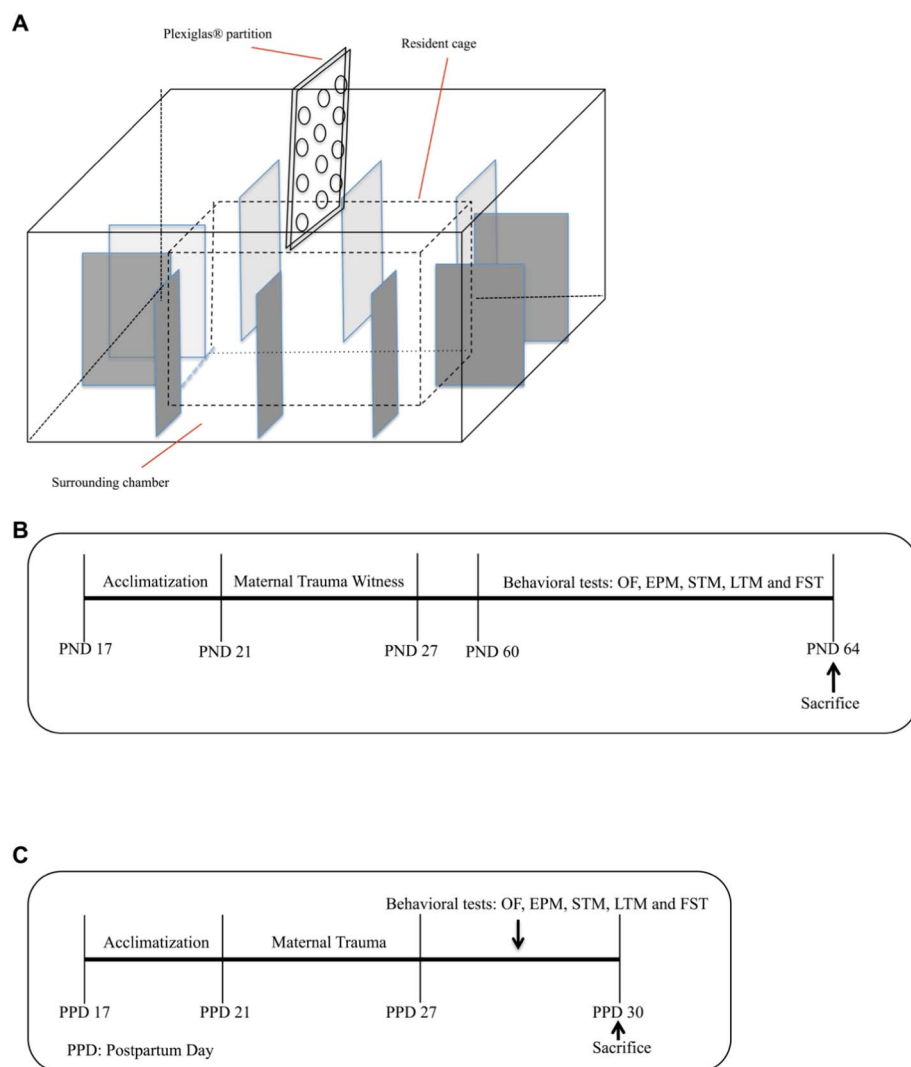


Fig. 1. A schematic representation of the maternal trauma witness apparatus comprising of a central enclosure where social defeat events occur and surrounding enclosures from where the social defeat events are witnessed by the pups (A), and the experimental design depicting the experimental protocol (B). Group designations are as follows: Pups at PND21 witnessed social defeat of dams (M-TW: maternal trauma witness), pups at PND21 witnessed only LE (LE-W: witness Long Evans rat only), pups at PND21 witnessed dams alone (W-D), pups at PND21 witnessed social defeat of a new female rat which is not a dam (F-TW: female trauma witness), pups at PND21 witnessed female rat only without social defeat (F-W), dams that underwent social defeat SD-D (social defeat-dams) and control females undergoing control exposures (CON). In addition to this, the experimental design depicting the experimental protocol to access the effects of maternal abuse on lactating female in the presence of her pups is shown in (C).

post-traumatic stress disorder (PTSD)-like behaviors (Patki et al., 2014, 2015). More recently, we published that early life stress in pups caused later life behavioral deficits in rats (Liu et al., 2017). In the present study, by combining the two approaches, we examined later life effect of early life maternal witness stress in rats. Briefly, a female Sprague-Dawley rat (dam: mother) was introduced into the cage of a Long Evans (LE) rat. The female rat (dam) underwent aggressive attacks from the LE rat. Natural litters at PND21 of the female rat were placed in separate chambers surrounding the cage witnessing these attacks. Pups were exposed to daily witness of repeated attacks between their mother and the male LE for 7 consecutive days, from PND21-PND27. Four and a half weeks later, when the pups became 60 days old (considered adults), behavioral outcomes of witnessing maternal stress were examined. It is important to clarify if memories of repeated witness experience of any fearful and/or traumatic event in early life are damaging for later behaviors, or is maternal stress witness central to modulation of later life behaviors? Several groups of rats were included to control for factors of fear unrelated to maternal stress witness, such as that of isolation from dams or induction of fearful stimuli from sighting of larger rats. One group of pups were made to repeatedly witness only the male aggressor rat in order to evaluate if the sighting of a large male rat is enough to induce behavioral impairments in pups. Another group of pups were made to witness a larger female rat for the same purpose. Third group of pups were allowed witness of a dam alone in isolation, in order to examine if maternal separation witness alone can cause deficits in pups. Fourth group of pups witnessed a new female

rat undergo social defeat. This female rat was not a dam, unrelated to pups. The purpose of inclusion of this group was to determine if witness of social defeat exposures of any female rat induces traumatic memories in pups which might elicit later life behavioral deficits. Finally, age-matched pups that did not witness maternal social defeat were also included as controls. Behavioral and cognitive analysis was also conducted in the dams after conclusion of social defeat procedure. Behavioral data of dams was compared with two other set of females. The purpose of this comparison was to examine if post-partum social defeat induced behavioral deficits in dams are related to post-partum trauma. One group of a non-lactating female rats did not undergo social defeat attacks, while another group of non-lactating female rats underwent social defeat attacks.

2. Methods

2.1. Animal housing and care

Upon arrival at the animal facility, rats were housed on a 12-h light/dark cycle in a climate-controlled room with food and water provided ad libitum. Experiments with rats were conducted in accordance with the NIH guidelines using protocols approved from the University of Houston Animal Care and Use Committee. Sprague-Dawley pups arrived on post-natal day (PND) 14 along with their dams. They were placed with the dams for 4 days for acclimatization. Before PND 18, pups and dams were housed together to allow bonding. Then age-

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