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Research report

Paradoxical enhancement of fear expression and extinction deficits in mice resilient to social defeat

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HIGHLIGHTS

- Mice can be characterized as susceptible or resilient after social defeat.
- Paradoxically, resilient mice display enhanced fear expression and poor extinction.
- These effects are not due to increased anxiety or poor behavioral flexibility.
- Mechanisms of resilience may leave animals vulnerable to maladaptive fear behavior.

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ABSTRACT

The exposure to stress has been associated with increased depressive and anxiety symptoms, yet not all individuals respond negatively to the experience of stress. Recent rodent social defeat models demonstrate similar individual differences in response to social stress. In particular, mice subjected to chronic social defeat have been characterized as being either "susceptible" or "resilient" by the level of social interaction following social defeat. Susceptibility is associated with lasting social avoidance as well as increased anxiety-like behavior, and depressive-like symptoms. Resilient animals, however, do not show social avoidance or increased depressive-like symptoms, but retain increased anxiety-like behavior. Thus, it is unclear what "resilience" as measured by social interaction represents in terms of an overall behavioral and physiological phenotype. Here, we use an acute social defeat procedure, which produces distinct behavioral phenotypes in social interaction with no apparent changes in anxiety-like behavior. Susceptible mice display lasting social avoidance, whereas resilient mice display normal social interaction. Susceptible mice also displayed deficits in fear extinction retention but had normal within-session extinction. Paradoxically, resilience was associated with enhanced fear expression, and severe deficits in fear extinction and extinction retention beyond that observed in susceptible mice. These effects in resilient mice were only apparent after the experience of social stress and were not due to impaired behavioral flexibility. These data suggest that mechanisms controlling resilience to acute social defeat as characterized by social interaction leave animals vulnerable to maladaptive fear behavior.

1. Introduction

Social stress, primarily in the form of conflict between individuals, is one of the most pervasive forms of stress experienced by many animal species, including humans. Exposure to social stress in humans and non-human animals often produces pronounced changes in physiology and behavior that may lead to the development of stress-related disorders. Although many individuals experience traumatic or stressful events during their lifetime, only a proportion of these individuals develop stress-related psychopathology. This underscores the importance of understanding the nature of resilience and vulnerability to stress-related psychopathology. For example, only a proportion of individuals who experience trauma develop post-traumatic stress disorder (PTSD), and the risk varies depending on the type of trauma experienced. People exposed to interpersonal violence have a greater propensity for developing PTSD than those exposed to nonpersonal trauma [1]. Rodent models of social defeat are ethologically relevant methods for examining behavioral and physiological responses to stress [2–6] and may have a unique ability to model the symptomatology of stress-related disorders like PTSD and depression [7–9]. Previously, we have demonstrated that behavioral responses to social defeat require amygdala-dependent plasticity, suggesting that social avoidance in response to social defeat may be a

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naturalistic measure of fear-motivated learning [6,9,10]. Associative fear learning and social defeat both produce behavioral effects that persist over a long period of time and we have shown that social avoidance following social defeat may be resistant to extinction [2,5,9–11]. Likewise, current hypotheses of PTSD suggest that the persistence of this disorder involves an inability to appropriately extinguish fear responses [12,13]. Thus, social defeat models may represent a unique way of examining associative fear learning mechanisms as well as the behavioral and physiological consequences of stress exposure, and may be well suited for modeling stress-related psychopathology.

Several recent studies have examined the effects of prior stress on associative and non-associative fear behavior in order to model the complex nature of PTSD symptomology [14–18]. For example, Knox et al. (2012) demonstrated specific fear extinction deficits in rats exposed to a single prolonged stress (SPS) procedure, modeling similar deficits in fear extinction observed in PTSD patients. Additional stressors including immobilization, exposure to shock, and exposure to predator odor produce similar, but varying effects in the acquisition, expression, and extinction of both associative and non-associative fear behavior [8,19–22]. However, less is known about the role of social stressors on associative fear behavior. Recently, studies have demonstrated conflicting findings regarding the effects of chronic social stress on fear learning [23–26]. For example, Yu et al. (2010) provided evidence of potentiated associative fear memory in mice after exposure to chronic social defeat stress. Additional evidence suggests similar effects of chronic social defeat stress including potentiated associative fear memory and impaired recall of fear extinction [25,26]. Inconsistent with the above findings, other reports demonstrated intact associative fear memory in mice after repeated exposure to social defeat [23]. Many of these studies have been used to model the complex nature of PTSD and other stress-related psychopathology. However, there remains a wide range of individual differences in the vulnerability to PTSD in humans and how these individual responses to stress contribute to the development of stress-related psychopathology is poorly understood.

Individual differences in vulnerability to the effects of social stress have been reported in recent chronic stress models [27–33]. Namely, following chronic social defeat stress, mice exhibit two distinct phenotypes that have been characterized as being either susceptible or unsusceptible to the defeat-induced avoidance observed in social interaction with a conspecific [31]. Susceptible mice exhibit a variety of deleterious symptoms following chronic social defeat that include anhedonia-like symptoms, increased anxiety-like behavior, elevated reactivity of the hypothalamic-pituitary-adrenal (HPA) axis, and stress-induced polydipsia [31,34,35]. In contrast, unsusceptible or resilient mice seldom exhibit the depressive-like behaviors of susceptible mice. Thus, this characterization of resilience appears to be well-suited to model resistance to depressive symptoms [31,35–37]. However, resilient mice also show increased anxiety-like behavior and elevated HPA axis reactivity [31]. Therefore, it remains unclear what resilience as measured by social interaction represents in terms of an overall behavioral and physiological phenotype, and how this may relate to resilience to other stress-related psychopathology like PTSD. In the present study, we take advantage of the ability to identify individual differences in stress responsiveness in an acute social defeat model, and also examine whether phenotypic differences in response to social defeat are associated with specific differences in associative fear learning and extinction. This enables us to examine how individual vulnerability to stress is related to alterations in associative fear and extinction, similar to what is observed in PTSD.

2. Material and methods

2.1. Animals

Six- to eight-week-old male C57BL/6J mice bred in our animal facility were used in all experimental procedures. Mice were housed in groups of four per cage until the beginning of each experiment. Mice were then housed individually and maintained on a 12:12 light/dark cycle from 7am to 7pm with *ad libitum* access to food and water. Four- to ten-month-old male CD1 mice bred in our animal facility were used as resident aggressors for social defeat training. Prior to the experiment CD1 mice were screened for their level of aggression and mice that attacked within two minutes were used for the experiment. All animal procedures were carried out in accordance with the National Institutes of Health guidelines and were approved by Kent State University Institutional Animal Care and Use (IACUC) Guidelines.

2.2. Behavioral manipulations

2.2.1. Social defeat stress

Adult male C57BL/6J mice were matched by weight and randomly assigned to defeat or control procedures. Mice assigned to the defeat group were subjected to social defeat stress by CD1 mice on two consecutive days. Non-defeated control mice were allowed sensory contact but no physical contact with a CD1 aggressor for the same duration of time. We used a modified procedure based on our previous acute social defeat studies in hamsters and recent chronic defeat studies in mice [2,31,35]. Briefly, an experimental mouse was placed into the home cage of a larger aggressive CD1 mouse and experienced 5 min of physical contact. A 55 min period of physical separation immediately followed. During separation, a perforated Plexiglas divider was positioned between the mice, dividing the cage in two equal halves, to allow sensory contact but preventing further physical contact. This procedure was repeated four times, with each defeat by a novel CD1 aggressor. Day 2 of the defeat procedure was exactly the same as Day 1 (Fig. 1A). Animals were monitored after every defeat session to ensure no serious wounds were incurred. During the defeats the number of attacks and latency to first submissive posture were videotaped and were scored later by an observer blind to experimental condition. An attack was defined as a lunge followed by a bite. Submissive behaviors that were recorded by intruders included upright defensive posture, side defensive posture, full submissive posture, and fleeing.

2.2.2. Social interaction testing

Social interaction testing followed 24 h after defeat to measure approach and avoidance behavior toward a novel non-threatening mouse (social target mouse). Social target mice were novel non-aggressive male CD1 mice as determined by pre-screening aggression testing. Testing was performed in a dimly lit room with four identical open field arenas (46 cm × 46 cm × 39 cm). A wire-mesh enclosure with Plexiglas frame (20 cm × 12 cm × 12 cm) was positioned against one of the four walls. The social interaction test consisted of two separate trials: Trial 1 (target absent) and Trial 2 (target present). In Trial 1, an experimental mouse was placed in the center of the arena and allotted 150 s to explore the novel environment in the absence of a social target mouse. After 150 s had elapsed, the experimental mouse was momentarily removed from the arena to position a social target mouse within the wire-mesh enclosure. In Trial 2, the experimental mouse was reintroduced into the center of the arena and allotted 150 s to explore in the presence of the social target mouse. A digital camera was positioned above the open field arena and automated tracking software (LimeLight; Coulbourn Instruments) was used to record locomotor activity