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Review

Sex differences in the effects of social defeat on brain and behavior in the California mouse: Insights from a monogamous rodent

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ABSTRACT

Women are nearly twice as likely as men to be diagnosed with major depressive disorder, yet the use of female animal models in studying the biological basis of depression lags behind that of males. The social defeat model uses social stress to generate depression-like symptoms in order to study the neurobiological mechanisms. In general, social defeat is difficult to apply in female rodents. However, male and female California mice (*Peromyscus californicus*) are territorial. This allows defeat to be studied in both sexes. Males exposed to defeat tend to exhibit proactive coping mechanisms and demonstrate aggression and reduced cognitive flexibility. Females exposed to defeat engage more in reactive coping mechanisms which is highlighted by social avoidance and low aggression. Importantly, effects of defeat on social interaction behavior in females is independent of adult gonadal steroids. These behavioral phenotypes are associated with sex-specific changes in arginine vasopressin (AVP) and oxytocin (OT), closely related peptides that regulate social behavior and stress reactivity. In brain regions associated with stress responses and social behavior, defeat induced long term decreases in AVP activity and increases in OT activity in males and females respectively. Intranasal OT administration was shown to mimic the effects of defeat-induced increases in endogenous OT activity, causing social withdrawal in undefeated females. This suggests that inhibition of OT activity could reduce the impact of stress on behavior in females. These results highlight the value of maintaining diverse rodent models in the search for sex-specific pharmacological approaches to treating mood disorders.

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1. Introduction

Mental illnesses such as anxiety, depression, and schizophrenia exact tremendous economic and personal costs, yet the front line treatments for many of these conditions have not changed significantly for the past 20 years [1,2]. Moreover, only a fraction of patients successfully respond to current treatment regimens [3]. However, basic research on the underlying neurobiological mechanisms for these conditions is providing new directions for the development of new treatments [4,5]. Indeed, a focus on the underlying mechanisms of heart disease and cancer has led to rational improvements in how these diseases are treated. Animal models, in which physiological mechanisms can be experimentally manipulated, are critical for determining causal mechanisms. Transgenic

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rodent models have been especially valuable for understanding how specific genes and neural circuits regulate behavioral phenotypes related to depression or anxiety. The advent of model systems sparked a convergence towards a handful of species; mainly C57Bl6 and a few rat lines. While these species are extraordinarily useful, the behavioral repertoire of these species has made certain questions less tractable. One of these questions is why depression and anxiety are more common in women versus men [6,7].

It has been known that depression and anxiety are more prevalent in women than men for over 2 decades [7]. Yet, an analysis in 2011 showed that less than 20% of basic neuroscience research publications include both males and females [8]. These analyses helped to raise awareness of a blind spot in the literature, and recent changes in science funding in the United States now compel the consideration of sex as a biological variable [9]. This has been a challenge for one of the most robust models of anxiety and depression disorders: social defeat stress. Exposure to psychosocial stress is an important risk factor for anxiety and depression [10,11], and social defeat stress has emerged as an important rodent model. Social defeat occurs when an individual loses in an aggressive encounter, which robustly induces behavioral phenotypes related to anxiety and depression. Almost all neuroscience studies using social defeat stress have used male rodents because adapting this protocol for females is challenging. Although lactating rats have been observed to be aggressive towards other females [12], attempts to perform defeat stress with C57Bl6 among females did not generate aggressive interactions [13]. The lack of aggression may be due to the lack of female territorial behavior in *Mus musculus*. Species in which females are more aggressive, such as Syrian hamsters (*Mesocricetus auratus*) and California mice (*Peromyscus californicus*) have proved more tractable for studying social defeat in females.

The genus *Peromyscus* consists of a diverse group of species that vary in their physiology, ecology, and behavior [14]. There is a wealth of natural history and social organization data for different species of *Peromyscus* [15], which allows one to select a species that is optimal for the question to be studied. The California mouse (*P. californicus*) in particular has proven valuable for examining the effects of social defeat stress in both males and females. The California mouse is a monogamous species and both males and females defend territories [16]. In laboratory resident-intruder tests, females aggressively confront an intruder placed in the home cage [17–19]. This behavioral response facilitated the development of a social defeat protocol for both males and females. Here we will discuss how studies using these protocols have provided insights into sex differences in the neuroendocrine responses to social stress. Determining how sex-specific changes in physiology mediate sex-specific behavioral responses to stress is an important step towards developing novel treatment approaches that account for sex as a biological variable.

2. The social defeat model of mood and anxiety disorders

Social defeat is generally regarded to be a more ethologically valid form of stress versus other lab-based approaches to stress such as restraint stress. Interestingly, although the mechanics of social stressors differ across species, the physiological and behavioral responses to social conflict are remarkably similar across many species of vertebrates, including humans [20–22]. An important aspect of social defeat protocols is the ability to randomly assign individuals to control or stress conditions. A focal animal assigned to stress conditions is placed in the home cage of unfamiliar resident of the same species. Under these conditions, the resident has a significant advantage and will almost always attack the intruder. In *Mus musculus*, a standard protocol involves short bouts of physical aggression followed by a period of sensory contact in which the focal mouse is separated from the resident by a perforated barrier. Under these conditions, ten days of defeat are usually performed to generate behavioral responses such anhedonia [23,24] and social avoidance [23,25,26]. In rats, fewer episodes of defeat are required to generate these responses [27,28]. Interestingly, the social withdrawal response to social defeat is evolutionarily conserved and has been reported in one form or another in birds [29], rodents [25,30,31], tree shrews [32,33] and primates [34]. An important aspect of the behavioral changes induced by defeat stress is that they can be reversed by chronic but not acute administration of antidepressant treatments [24,25]. This suggests that the underlying mechanisms of antidepressant action in the defeat model are similar to its therapeutic effects in humans and contrasts with the forced swim test in which acute antidepressant treatment can reduce immobility. Thus while the forced swim test predicts antidepressant efficacy, it provides less insight into underlying mechanisms [21].

Although social defeat stress reliably produces behavioral phenotypes that respond in a pharmacologically valid manner to antidepressants, an important weakness has been the difficulty in applying this approach to females. As mentioned previously, intrafemale aggression is minimal in *Mus musculus* [35]. However, other species have proved to be more conducive to studying females. For example female Syrian hamsters are actually more aggressive than males [36]. Here the intense aggression of females may actually blunt the behavioral effects of defeat stress which are weaker and more short-lived compared to those observed in males [37,38]. This is consistent with other data from hamsters that more aggressive individuals are more resilient to social stressors [39]. In contrast, both male and female California mice exposed to defeat show long lasting changes in behavior and brain function.

3. California mouse model of social defeat

The California mouse model of social defeat is based on naturally occurring territorial behavior in males and females of this species [40]. Male residents are vasectomized and paired with females, which results in higher levels of aggression with lower variability than virgin mice. Each episode of defeat is terminated after the resident attacks the intruder seven times or after seven min, whichever comes first [41]. This protocol normalizes the intensity of aggression that males and females are exposed to and prevents injury to focal mice. During episodes of defeat, fewer sex differences in behavior are observed. Males and females show similar rates of freezing when confronted with an aggressive resident, although on average females exhibit more attempts to flee from the resident [42]. Males and females also show signs of a conditioned anxiety response after two episodes of defeat. Immediately prior to a third episode of social defeat, both males and females show increases in autogrooming behavior upon transfer to the testing room [43]. Elevated autogrooming behavior is an anxiety-like behavior in rodents [44]. In contrast to the short-term effects of defeat on behavior, robust sex differences are observed in the long-term effects of defeat on behavior.

When examining the long-term effects of defeat on behavior, male behavioral phenotypes are more consistent with proactive coping strategies in which stressors are more directly confronted while female behavioral phenotypes are more consistent with reactive coping strategies in which stressors are avoided [45] (Fig. 1). For example when focal mice are confronted with an intruder in the resident-intruder test, stressed males showed levels of aggression that were similar to control males while stressed females showed no aggression [46]. Reduced levels of aggression are thought to be linked to increased cognitive flexibility, as the individual only attacks when necessary [45]. Consistent with this idea, defeated