Seminars in Cell & Developmental Biology 61 (2017) 92–98

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

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

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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ARTICLE INFO

Article history:
Received 29 May 2016
Received in revised form 28 June 2016
Accepted 29 June 2016
Available online 30 June 2016

Keywords:
Aggression
Nonapeptides
Peromyscus
Sex differences
Social behavior
Social defeat

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.

Contents

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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http://dx.doi.org/10.1016/j.semcdb.2016.06.021
1084-9521/

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

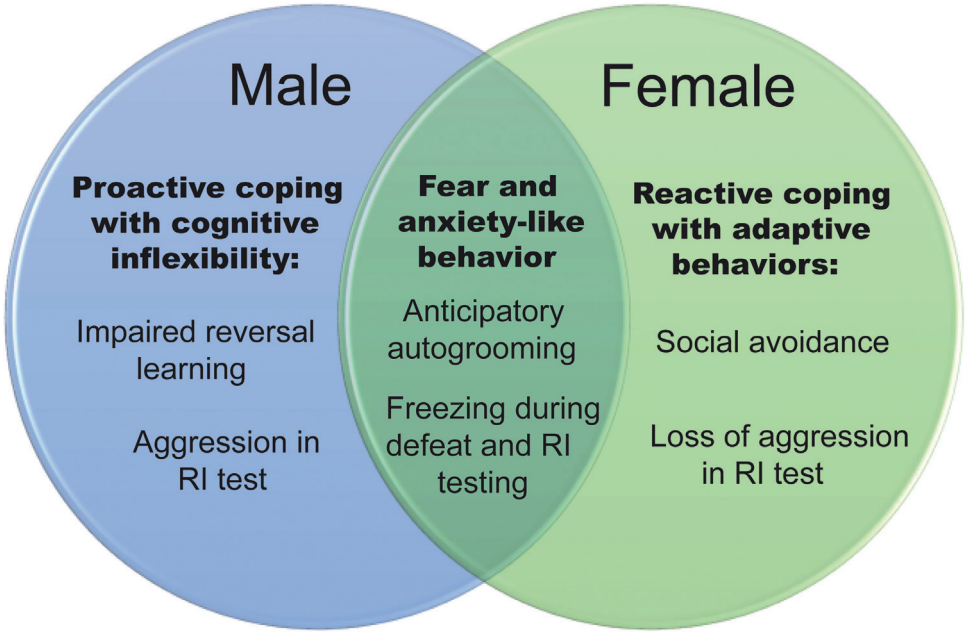

Fig. 1. Venn diagram demonstrating general and sex-specific behavioral responses to social defeat. Males tend toward a proactive coping approach highlighted by weak cognitive flexibility shown by poor reversal learning and unaltered levels of aggression in the resident-intruder test (RI). In contrast, females, exhibit more of a reactive coping approach with significant alterations in behavioral tendencies including reduced social approach to a novel conspecific (social avoidance) and a near complete loss of aggression in the RI test. Both sexes demonstrate similar fear and anxiety-like behaviors in response to the threat of an agonistic encounter, engaging in elevated autogrooming when brought into the room where social defeat had previously occurred and pronounced freezing during both social defeat itself and RI testing.

male California mice made more errors during a reversal learning task whereas stressed females made fewer errors [47]. Deficits in cognitive flexibility are a common feature of mood disorders [48]. In addition, men have been reported to have a greater tendency than women to engage in rumination and perseveration, and male ruminators are prone to greater cognitive inflexibility than non-ruminators [48]. While defeat stress did not affect the performance of female California mice in a reversal task, robust changes in behavior were observed in social contexts.

For females, social defeat has robust effects on behavior in the social interaction test. In this test the focal mouse has an opportunity to approach an unfamiliar "target" mouse of the same sex confined to a wire cage. The "target" mouse usually generates a very strong approach response across many rodent species, including California mice. In male mice and rats, defeat stress can reduce social interaction behavior and chronic (but not acute) antidepressant treatment can reverse this effect. This pharmacological validity has made the social interaction test a useful behavioral assay of social motivation. Defeat stress reduces social interaction behavior in female California mice [31,43], and this effect can be seen as long as ten weeks after the last episode of defeat [49]. Social interaction behavior in stressed females can be restored with four weeks of daily sertraline treatment [50]. In contrast, stressed male California mice show unaltered levels of social interaction behavior unless treated with some form of peripheral [49] or intracranial [51] injection immediately before testing. Thus while defeat itself does not reduce male social interaction behavior, it appears to make the circuitry modulating this behavior more sensitive to acute stressors. Although gonadal hormones are often an important source of sex differences in behavior, sex differences in social interaction behavior appear to be independent of gonadal hormones. Stress-induced decreases in social interaction behavior were observed across different stages of the estrous cycle [31]. Furthermore, gonadectomy did not alter the effect of defeat stress on social interaction behavior in males or females [42]. However, indirect evidence suggests that gonadal steroids may act early in life to organize sex differences in the circuitry that mediates social withdrawal in stressed females. Female California mice raised on corncob bedding show a blunted social withdrawal phenotype after [41]. Interestingly, corncob bedding contains estrogen-like tetrahydrofurandiols (THF-diols), which can alter estrogen signaling and may have important effects on the organization of sex differences [52]. California mice consume the corncob bedding, which in turn increases THF-diols in their blood and alters neurobiological pathways related to stress and social behavior [53]. Mice raised on corncob bedding also had reduced estrogen receptor expression across several brain regions. Estrogen receptors have been shown to impact the development of neuropeptide signaling systems such as oxytocin (OT) and vasopressin (AVP) [54].

4. Short term effects of defeat on OT and AVP: similarities between the sexes

OT and AVP are referred to as nonapeptides in reference to their composition of nine amino acid residues [55]. These two nonapeptides differ by only two residues [56] which results in a high degree of promiscuity in binding to receptors [57]. Thus, experimental infusions of OT or AVP can induce similar behavior effects [58–61]. Social reward, hierarchy, and memory are behavioral processes that are sensitive to both OT and AVP [62–70]. An unusual case is male offensive aggression, in which AVP facilitates [71–75] and OT inhibits [76,77] these behaviors. This could be because the receptors facilitating or inhibiting aggression are segregated anatomically. For example, OT acting in the central amygdala inhibits male aggression [78] while AVP acting in the anterior hypothalamus facilitates aggression [79]. More direct anatomical comparisons are needed to fully understand these effects. It is often assumed that AVP facilitates social approach as a first step towards other behavioral interactions such as sexual or aggressive behavior. However, evidence has accumulated that OT and AVP can also facilitate social avoidance [80]. This has required a reevaluation of social approach hypotheses of nonapeptides. Given that nonapeptides are so well positioned to integrate stress responses with responses to

social stimuli in a sex-dependent manner we conducted several studies to explore how OT and AVP respond to the social defeat paradigm.

In general the activity of OT and AVP neurons within the paraventricular nucleus (PVN) showed similar responses in males and females when assessed with fluorescent immunohistochemistry [49,46]. Both OT and AVP neurons in the PVN had more colocalizations after a third episode of social defeat in males and females. However, after one episode of defeat stress males show increased OT/c-fos colocalizations whereas females did not. While it is not clear that this sex difference has short-term impacts on behavior, more consistent responses of OT neurons during defeat in males might impact responses of the hypothalamic-pituitary-adrenal (HPA) axis. Oxytocin can inhibit glucocorticoid responses to stressors [82,83]. After a third episode of social defeat, female California mouse corticosterone levels were significantly higher than controls whereas this response was blunted in males [42]. Similar sex differences in HPA responses have been observed in other species of rodents [84–86] (but see Refs. [87,88]). However, it's unlikely that sex differences in HPA function during defeat mediate sex differences in social withdrawal. Gonadectomy blunted corticosterone responses to defeat in females but had no effect on the development of social withdrawal. Currently, the behavioral significance of the acute HPA responses is still uncertain.

5. Long term effects of defeat on OT and AVP: sex differences

Social defeat has long lasting and reproducible sex-dependent effects on OT and AVP systems (see Table 1 for a summary). Social defeat significantly decreases AVP cell counts within the caudal PVN of males for up to ten weeks, while having no effect in females [46]. This is accompanied by a decrease in *Avp* mRNA expression within the male PVN pointing to an overall inhibition of synthesis [46]. Unlike female counterparts, defeated male California mice exhibit elevated baseline corticosterone [31] and it has been suggested that elevated glucocorticoid levels following social stress may inhibit the AVP system [89]. Defeated males also have significantly lower plasma levels of AVP following social interaction testing than do controls. This suggests that reduced AVP synthesis may diminish the capacity for AVP release from the PVN [46]. Although stressed females showed few changes in AVP immunoreactivity or expression, OT systems were strongly affected.

In the rostral PVN, defeat increased the percentage of OT/c-fos colocalizations in females across a number of studies, particularly in social contexts [49]. This apparent increase in OT activity occurred in conjunction with decreased OT protein staining and no change in mRNA expression. Taken together, this combination of results may indicate that defeat enhances OT release from PVN OT neurons without affecting synthesis and thus reducing the number of OT neurons detectable by immunohistochemistry [49]. Moreover, a striking association emerged in which higher percentages of OT/c-fos colocalizations in the PVN were linked to lower preferences for a social over non-social stimulus in both females [49]. This link was observed less consistently in males. These results suggest that context-dependent increases in activation of rostral PVN OT may inhibit social approach, particularly in females. Interestingly, the effect of social defeat on OT neurons in another nucleus was less context-dependent.

A group of OT neurons in the bed nucleus of the stria terminalis (BNST) was found to show robust changes to defeat. The BNST is as an important nucleus mediating threat detection and psychopathology [91], and this population of OT neurons within the medioventral bed nucleus stria terminalis (BNSTmv) is evolutionarily conserved across rodent [92,93] and primate [94,95] species. Defeated females displayed an increase in the percentage of OT/c-fos colocalizations in both social and nonsocial contexts [49]. This effect differs from the rostral PVN in which increases in OT/c-fos colocalizations were only observed in social contexts. In females, stress-induced increases in OT/c-fos colocalizations coincided with increases in OT-ir perikarya and mRNA expression. The effect on OT cell number was observed in animals at both two and ten weeks following defeat, while the mRNA effect was examined only in animals at the two-week time point. Across the rostral PVN and BNSTmv the data suggest that in females, defeat increases OT activity in brain regions that modulate social behavior. This might appear counterintuitive, because stressed females had reduced social interaction behavior. Although OT is typically considered to have prosocial effects, there is growing appreciation that the effects of OT on sociability are multivalenced.

6. Sex-specific effects of intranasal OT on social behavior

To test the behavioral effects of OT we conducted intranasal OT studies in California mice. We chose the intranasal route of administration because this is how OT is being administered in human clinical trials [96]. First we administered intranasal OT to defeated California mice at a dose comparable to that used in human clinical studies. Males treated with OT showed a non-selective increase in approach toward a wire cage regardless of whether it contained a social stimulus, while no effect was observed in females [49]. When the same dose was administered to mice that were naïve to defeat, males displayed no change in approach. However, females showed significant reductions in time investigating a novel mouse. This effect was strikingly similar the effect of defeat stress. Thus the behavioral effects of intranasal OT are pointedly different in males and females. In the social interaction test, the effect of intranasal OT in females strongly resembled the effect of social defeat. This may provide a new perspective on how to interpret correlational data from human studies.

A number of studies have identified elevated plasma levels of OT in women diagnosed with PTSD or depression [97–99]. One interpretation for this difference is that elevated OT represents a physiological coping mechanism. However, the results in California mice suggest an alternative hypothesis: that elevated OT function may be a contributing factor to certain symptoms of mood or anxiety disorders. Results from other rodent studies provide insights into the neural circuits that could mediate inhibitory effects of OT on social behavior. The lateral septum is a nucleus in which higher levels of oxytocin receptor (OTR) binding correspond with reduced female affiliation in meadow voles (*Microtus pennsylvanicus*) [100] and tuco-tucos (*Ctenomys*) [101]. Mechanistic studies suggest that OTR in the lateral septum have important effects on the salience of social cues. For example, specific deletion of OTR in lateral septum using the Cre/*loxP* system blocked the effects of defeat stress on social interaction behavior [102]. Deletion of OTR in lateral septum also inhibited the extinction of defeat induced anxiety following more positive social interactions [103]. Although previous studies have demonstrated that PVN and BNSTmv neurons project to the lateral septum, it is unclear whether any of these projecting cells are OT-ergic. Also unclear is whether variability in the rate of OT release plays a role in determining the ultimate behavioral output. For example, phasic but not tonic activity of dopamine neurons in the ventral tegmental area is linked with reduced social interaction behavior [104–106]. Although the electrophysiological properties of OT neurons have been studied [107], they have not been linked to variation in social behavior. Regardless, it is clear that additional knowledge on the electrophysiological properties of OT neurons as well as their projections will be important for understanding the varied behavioral effects of OT. Eventually it will be necessary

Table 1
Effects of social defeat on arginine vasopressin (AVP) and oxytocin (OT) systems in California mice. Social defeat decreased AVP cell counts and mRNA levels in the paraventricular nucleus (PVN) of males while having no effects of the percentage of c-fos/OT cololcalizations (Colo%). In females defeat decreased OT cell counts in the PVN and increased their colocalizations with c-fos without affecting mRNA levels suggesting a change in OT release not synthesis. Finally, social defeat increased OT cell counts, colocalizations, and mRNA levels in the medioventral bed nucleus of the stria terminalis (BNST) of females suggesting enhanced synthesis and release.

Long Term Effects of Defeat on Nonapeptides								
		Paraventricular Nucleus			Medioventral BNST			References
Transmitter	Sex	Cell #	Colo%	mRNA	Cell #	Colo%	mRNA	
AVP	Female	–	–*	–	None detectable			Steinman et al. [46,49]
	Male	↓	–*	↓				
OT	Female	↓	↑	–	↑	↑	↑	Steinman et al. [49]
	Male	–	–	–	–	–	–	

↓ decrease, ↑ increase, – no change, *data not previously reported from the study.

to understand how experience can alter these parameters, which should provide perspective on the context-dependent effects of OT [108].

Familiarity with the environmental context is an important factor influencing the effects of OT on behavior and cognition. For example, the same dose of OT that reduced social approach in females during social interaction testing had anxiolytic properties in the RI test, significantly reducing this freezing in defeated mice of both sexes [49]. The environment in the social interaction test is unfamiliar whereas the RI test takes place in the home cage. For males, OT was anxiolytic in the home cage but not in an unfamiliar environment. These results are consistent with how defeat affects behavior, because defeat affects female but not male behavior in the social interaction test. It is possible that this sex difference represents the generalization of risk from one environment to a novel environment, which is thought to be an important mechanism in PTSD [109]. This would be consistent with another study in which female rats exposed to foot shock generalized fear memories to novel environments more robustly and for longer periods of time than male counterparts [110]. Although the mechanisms for these sex differences are not completely understood, these results support the hypothesis the mechanisms of susceptibility and resilience to stress-induced psychiatric disorders have important differences between males and females [111].

7. Conclusions

The social defeat model has contributed greatly to the fields of neuroscience and psychiatry by providing insight into the physiological and behavioral effects of social stress across many broad groups of animals. Nevertheless, its historically limited success in female rodents has created a heavily male-biased literature that ultimately struggles to provide insights in to the mechanisms contributing to sex differences in behavioral responses to stress. The inherent territoriality expressed in both sexes of California mice has made this species effective in understanding the sex specific effects of social defeat on the brain and behavior. An important finding is that sex differences are more likely to emerge long after stress occurs, suggesting there may be important differences in epigenetic responses to stress. The examination of nonapeptide system responses of California mice to social defeat has revealed that distinct but closely related neural circuits show sex-specific responses. Most of these changes interact with environmental and social contexts to affect behavior. The development of new tools such as a California mouse brain atlas (brainmaps.org) and brain transcriptomes should facilitate further mechanistic studies to complement ongoing innovative work using more conventional mouse and rat models. Together, these research programs have the potential to provide novel insights in to the neurobiological mechanisms that mediate the effects of stress on behavior. For example, our recent results suggest that the inhibition of OT signaling could reverse some of the behavioral effects of stress in females. It's unlikely this hypothesis could have been developed from a male social defeat program, as OT reduced the effects of stress on behavior in males. These findings highlight the need to maintain a diverse collection of animal models in the search for underlying mechanisms of stress-induced psychiatric disorders.

Acknowledgments

MQS was supported by T32 AA007456 and BCT was supported by R01 MH103322 during the preparation of this work.

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