Mean Girls: Social Stress Models for Female Rodents

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Contents

Abstract Social stressors are known to have strong negative impacts on mental health. There is a long history of preclinical social defeat stress studies in rodents focusing on males that has produced important insights into the neural mechanisms

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that modulate depression- and anxiety-related behavior. Despite these impressive results, a historical weakness of rodent social stress models has been an under-representation of studies in females. This is problematic because rates of depression and anxiety are higher in women versus men. Recently there has been a surge of interest in adapting social stress methods for female rodents. Here we review new rodent models that have investigated numerous facets of social stress in females. The different models have different strengths and weaknesses, with some model systems having stronger ethological validity with other models having better access to molecular tools to manipulate neural circuits. Continued use and refinement of these complementary models will be critical for addressing gaps in understanding the function of neural circuits modulating depression- and anxiety-related behavior in females.

Keywords Anhedonia · Hamster · Oxytocin · Peromyscus · Sex differences · Vole · Witness defeat

1 Introduction

Social stressors have become a main focus as risk factors for adverse mental health outcomes. Although treatments are available for mental illnesses such as depression and anxiety, many individuals do not respond to existing therapies (Fava 2003; Akil et al. 2018). A unifying theme in medicine is that understanding the underlying mechanisms of diseases can provide a rational path for the development of novel treatments. Animal models can play a key role in this process because of the power to perform mechanistic experiments that can help us understand results from clinical studies. Social stressors can take several forms, such as social isolation (Weintraub et al. 2010), the loss of a familiar partner (McNeal et al. 2014), or aggressive interactions (Kudryavtseva et al. 1991). Social stress models based on aggressive interactions have proved amenable to study. This is because many of the behavioral and physiological effects of stress exposure are evolutionarily conserved. In particular, the losers of aggressive contests across fish, birds, rodents, and primates generate similar physiological responses such as release of adrenal hormones and long-lasting changes in social behavior. Although social stressors can take several forms, in this chapter we will primarily focus on the utility of social defeat models. Unlike more conventional stress models such as restraint stress (Grissom and Bhatnagar 2009), most individuals do not habituate to social stressors. This may explain why certain social stress phenotypes such as social avoidance can be replicated in different species and labs around the world (Kudryavtseva et al. 1991; Blanchard et al. 1993; Tornatzky and Miczek 1993; Martinez et al. 1998; Huhman 2006). Despite these strengths, social stress models have historically had an important weakness: under-representation of studies on females. This is problematic because of the over-representation of some mental illnesses in women compared to men, such as social anxiety disorder, generalized anxiety disorder, and major

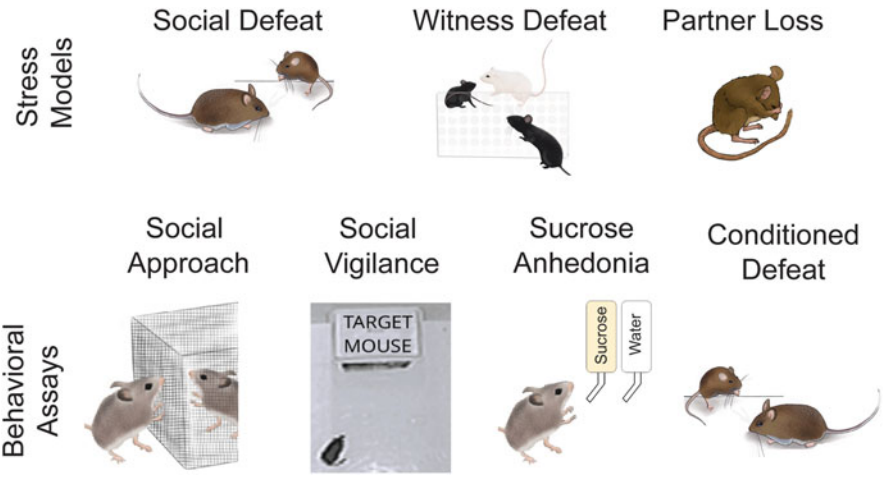

Fig. 1 Methods for studying social defeat have been developed for several different species. Social stress can be induced via direct physical social defeat or witness defeat protocols. Partner loss in monogamous species is another important form of social stress with translational relevance. Different behavioral assays allow for systematic quantification of the impact of social defeat in different contexts. Social interaction tests assess behaviors in novel or unfamiliar contexts while conditioned defeat and sucrose anhedonia tests are important assessment of behavior in familiar environments

depression (McLean et al. 2011; Bangasser and Valentino 2014; Asher and Aderka 2018). An additional problem is that therapeutic approaches to mental illness can act differently in men and women (Dalla et al. 2010; Williams and Trainor 2018). Thus, even if stress has similar behavioral effects in males and females, the underlying mechanisms could be different.

The over-representation of males has not been unique to studies of stress biology (Beery and Zucker 2011; Prendergast et al. 2014), prompting an increased focus across biomedical research to test hypotheses in both males and females (Tannenbaum et al. 2016; Miller et al. 2017). While there is still progress to be made (Mamlouk et al. 2020), numerous new social stress models have been developed in the past decade that allow for the study of females. Some model systems rely on species with social systems in which females engage in robust aggression. Increased female aggression in these species (hamsters, California mice, prairie voles) differs from the more conventional rat and mouse lines used for behavioral neuroscience research, in which inter-female aggressive interactions are generally muted. However, creative experimental designs, often under more ethologically relevant conditions have been developed in domesticated mice and rats. These methods provide access to powerful molecular tools for studying neural circuits. Here we review female social stress models in behavioral neuroscience (Fig. 1) and break down key findings within each approach. We also consider the strengths and weaknesses of each model with an appreciation that no single model system can fully capture the complexities of stress-induced mental illnesses (Table 1). It is

Table 1 Strengths of weaknesses of social stress models across species

Species	Strengths	Weaknesses
Syrian hamster	Strong ethological validity for females	Few molecular tools currently available
	Well defined neurocircuitry in males	
	Males and females have been directly compared	
	New transgenic animals produced	
California mouse	Strong ethological validity for females	Few molecular tools currently available
	Pharmacological validity for social interaction test	
	Stonger social behavior effect in females aligns with clinical prevalence of anxiety in women	
	Males and females have been directly compared	
Prairie voles/ Mandarin voles	Strong ethological validity for females	Few molecular tools currently available
	Males and females have been directly compared	
	Strong potential for study of partner loss	
	New methods for molecular tool development transgenic animals produced	
Domestic mice	Standardized protocols for males have been widely used	Some models have low ethological validity
	New complementary methods have been developed to study social stress in females	
	Ability to study suceptible and unsusceptible phenotypes	
	Many molecular tools available for studying neural circuits	
Rats	New complementary methods have been developed to study social stress in females	Effects of social defeat in adult females are generally weak
	Larger body size facilitates approaches such as microdialysis or electrophysiology	
	Effects of adolescent stress on behavior are well described in males and females	
	Excellent potential for use in operant conditioning or substance abuse contexts	

important to note that recent developments in chronic variable stress protocols have emerged as an important category of models for studying stress-induced behavioral and neurobiological phenotypes (Hodes et al. 2015; Williams et al. 2020b). However, we will limit the focus to recent developments in social stress models adapted for females.

2 Syrian Hamsters

The social behavior of Syrian hamsters (*Mesocricetus auratus*) has been studied for decades (Powers and Valenstein 1972; Garrett and Campbell 1980; Kollack-Walker and Newman 1995). This species is known for its relatively intense aggressive behavior (Johnston 1975). Originating in the far western regions of Asia (Siegel 1985) Syrian hamsters are solitary, with females engaging in offspring care alone without interacting with a mate (Gattermann et al. 2001). This social organization likely contributes to a reduced impact of social isolation on behavior in this species (Ross et al. 2017). Unlike many species of rodents, female Syrian hamsters engage in territorial aggression, and females are actually more aggressive than males when not sexually receptive (Payne and Swanson 1970). This trait likely impacts their responses to social stress. The unique social organization provided an excellent opportunity to apply techniques to study social stress in males and females (Huhman et al. 2003).

2.1 Conditioned Defeat

Social defeat methods in hamsters were first developed in males (Potegal et al. 1993). In this paradigm, a resident-intruder test is used in which the focal animal is introduced into the home-cage of an aggressive, same-sex hamster. This can occur once or on consecutive days. The most common behavioral assay is performed a day later when the focal hamster is tested in the home-cage as a resident with a non-aggressive intruder (Faruzzi et al. 2005; Solomon 2017). Typically, an unstressed hamster will engage in aggressive behaviors including chasing, biting, lunging, and upright or side attacks as well as social investigation. In contrast, stressed hamsters are more likely to exhibit defensive behaviors such as fleeing, submissive postures, tail lifts, and upright/side defense. This behavioral phenotype is referred to as "conditioned defeat" and resembles certain phenotypes associated with stress-related mental illness (Huhman 2006). These methods have been used in male hamsters to identify neural circuits involved in the acquisition and expression of these behaviors including the bed nucleus of the stria terminalis (BNST), nucleus accumbens (NAc), and basolateral amygdala (Markham et al. 2009; Cooper and Huhman 2010; Gray et al. 2015). More recently, these methods have been applied to females, resulting in unique phenotypes from males.

Interestingly, the effects of defeat on behavior are less profound in females than in males (Huhman et al. 2003). Males often show greater amounts of submissive behaviors like tail lifts and fleeing, whereas these responses were blunted in females. Stressed females showed more aggressive behaviors, indicating that these territorial behaviors in females are less sensitive to the effects losing aggressive encounters. A major question is how this occurs. Studies examining the effects of defeat on behavior across the 4-day estrous cycle suggest that gonadal hormones are not a

key mechanism. While stressed females showed higher levels of aggression during stages of the estrous cycle when estrogens were low, submissive behaviors were muted across all stages of the cycle (Solomon et al. 2007). In this same study, researchers saw that both defeated and non-defeated females tested on the day of estrus displayed lordosis towards female intruders. The unexpected display of lordosis to another female has been documented previously (Johnston 1977), but its function is unknown. Thus, despite these interesting patterns, gonadal hormones in adults do not appear to be a key causal mechanism. Instead, elevated aggression levels in female hamsters may interfere with the display of submissive behaviors.

In male hamsters, social hierarchy plays a role in resilience to conditioned defeat where defeat stress induces stronger effects on subordinate males than dominant males (Morrison et al. 2012). As females are more aggressive than males (Payne and Swanson 1970), this may explain why they are less sensitive to defeat in resident-intruder tests. In resident-intruder tests, the resident has what is referred to as a "home advantage" or "residence effect" – which describes the increased ability to win an aggressive encounter when an animal is on their own territory which is seen in humans and rodents alike (Carre et al. 2006; Fuxjager et al. 2010). When this home advantage is removed, female Syrian hamsters are more sensitive to defeat stress. In one study, social defeat induced social avoidance in females that were tested in a novel environment with a stimulus hamster confined to a small wire cage (Rosenhauer et al. 2017). Thus, in novel environments, stressed females respond more similarly to males. Further research is needed to understand the underlying mechanisms for these intriguing sex differences. Interestingly, defeat stress has distinct effects on transcription in the basolateral amygdala (BLA).

The BLA is a key brain region for the formation of conditioned defeat phenotypes in males (Jasnow et al. 2005; Dulka et al. 2020). When RNAseq was used to compare effects of defeat on gene expression in males and females, there was little to no overlap in gene expression across social status between the sexes (McCann et al. 2019). Essentially, sex-specific differences in gene expression were observed across dominants, subordinates, or in unstressed controls. These sex-specific transcriptional responses to hierarchy formation are consistent with previous transcriptional analyses in rodents. Sex-specific transcriptional responses to social stress have been observed in the hippocampus (Marrocco et al. 2017), NAc (Hodes et al. 2015) and amygdala (Walker et al. 2020) as well as in humans diagnosed with stress-related mental illnesses such as depression (Labonté et al. 2017). Although each of these studies focuses on different brain regions, the broad pattern of sex-specific transcriptional patterns are consistent. The sex-specific transcriptional responses to defeat in female hamsters suggest that further mechanistic study of this region is warranted. Indeed, sex-specific mechanisms of behavior have been documented for other behaviors in hamsters. For example, inhibition of V1a receptors within the anterior hypothalamus reduces aggression in males but increases aggression in females (Gutzler et al. 2010). These studies are important because they show that even when the sexes are behaving similarly, there can be sex differences in underlying mechanisms.

2.2 Summary

Strengths of the hamster social defeat model include strong ethological validity of aggressive behavior in females and a deep understanding of neural circuits underlying conditioned defeat behavioral phenotypes in males. Currently there are relatively few genetic tools for studying hamsters, although this is beginning to change. Hamsters are an important model species for other biomedical fields such as immunology (Safronetz et al. 2012), which has incentivized the development of genetic tools for this species (Fan et al. 2014). Recently generated V1a receptor knockout hamsters showed that adult males and females were more aggressive than wild types (Taylor et al. 2019). While these results were consistent with previous work in females, the results in males were unexpected as V1a receptors generally promote aggression in males. This suggests that V1a receptors may have important developmental effects on aggressive behaviors. These data highlight the potential for developing new transgenic hamster lines.

Currently, it is unclear how or why females show weaker responses to social defeat in resident-intruder tests. However, stressed females do exhibit social avoidance phenotypes when tested in an unfamiliar environment. While this phenotype is similar to males, stress has sex-specific effects on transcriptional responses within the BLA (McCann et al. 2019), which is known to play a critical role in behavioral responses to stress. This suggests that further study of the neural circuits impacted by social defeat in female Syrian hamsters has the potential to identify sex-specific mechanisms of anxiety- and depression-related behaviors.

3 California Mice

The California mouse (*Peromyscus californicus*) is another species in which females are aggressive towards other females (Davis and Marler 2003). This species is monogamous (Ribble 1991) and has long been studied as a model for understanding neuroendocrine mechanisms of parental care (Gleason and Marler 2010; Harris et al. 2013; Hyer et al. 2017) and aggression (Oyegbile and Marler 2005; Fuxjager et al. 2010). Besides elevated aggression levels in this species, a clue that California mice could be useful for studying social stress came from the observation that female residents had higher corticosterone levels following an aggressive encounter than males (Trainor et al. 2010). This suggested that social conflict in females might have stronger physiological effects in females versus males. Systematic characterizations of behavior show that the effects of social defeat stress are context-specific with females showing stronger changes in unfamiliar social contexts and males showing stronger deficits in complex cognitive tasks. We will also review the impact of a different form of stress, separation of pair-bonded mice.

3.1 Social Defeat

A standard protocol uses three episodes of defeat across 3 days with only one defeat session per day with a same-sex opponent (Trainor et al. 2011). If each episode is limited to 7 min or stopped after the resident attacks the focal mouse seven times, there is no difference in the number of attacks males and females receive. During the defeat episodes, both female and male mice display equal levels of freezing and defensive behaviors, although escape behaviors are more frequent in females than males (Trainor et al. 2013). This is reminiscent of "darting" behavior in female rats, in which females attempt to escape footshocks instead of freezing (Gruene et al. 2015). Interestingly this more active coping behavior in females is associated with increased corticosterone levels immediately following defeat, an effect that is dependent on ovarian hormones (Trainor et al. 2013). The long-term effects of social defeat on behavior have been examined using a wide range of tests. In general, the effects of defeat on social behavior are stronger in females whereas males exhibit stronger effects of defeat in non-social contexts.

3.2 Social Interaction Test

A social interaction test is the most commonly used behavioral assay for California mice (Greenberg et al. 2014). Alterations in social approach behavior have translational relevance because withdrawal from social situations is a common symptom for both depression and anxiety disorders (Saris et al. 2017). In social defeat models, social interaction tests also have pharmacological validity because stress reduces approach to an unfamiliar stimulus mouse, and this effect is reversed by chronic but not acute antidepressant treatment (Berton et al. 2006). Finally, effects of social defeat on behavior in this assay can last for many weeks, similar to the chronic nature of depression and anxiety. The test used for California mice has three distinct phases: open field, acclimation, and interaction. First the focal mouse is placed in an empty, novel open field arena and the time spent in the center of the arena and total distance traveled are measured. The arena is much larger (almost 1 m long) than typical apparatuses for social behavior. For comparison, a typical three-chambered test for social interaction uses chambers that are 20 cm long (Yang et al. 2011). Next, an empty wire cage is introduced into the open arena against one of the walls. This acclimation phase can serve as a novel object test, as mice will typically investigate the empty cage. Video tracking software is used to track the time spent within 8 cm of the empty cage. Finally, an unfamiliar same-sex conspecific is placed into the wire cage for 3 min. The use of a wire cage where the focal mouse can see, smell, and interact with the target mouse is a key aspect of the test, as the use of a perforated plexiglass cages results in much lower levels of social approach. During the interaction phase, social approach is defined as the time spent within 8 cm of the target mouse. The large arena size facilitates the quantification of a second variable, social

vigilance. Social vigilance is defined as the time the focal mouse spends outside of the interaction zone (within 8 cm of target mouse) with its head oriented towards the unfamiliar mouse. A combination of avoidance and vigilance is characteristic of behavioral inhibition in children (Fox et al. 2005), which is an important risk factor for the development of anxiety disorders in adults (Clauss and Blackford 2012). The effects of social defeat on these behaviors are sex-dependent.

Female California mice are particularly sensitive to the long-term effects of defeat stress. Effects of defeat on social approach are relatively weak 1 day after the last episode of defeat, but become stronger 4 weeks later, as females spend less time interacting with the target mouse compared to males (Trainor et al. 2011). This sex difference does not vary across the ovarian cycle and is not affected by ovariectomy (Trainor et al. 2013). Although chronic stressors have been linked to disrupted ovarian cycles in rodents (Pollard et al. 1975) and humans (Bae et al. 2018), this is not observed in studies of California mice. This is likely due to the use of three relatively brief episodes of social defeat. Thus, it is instructive that phenotypes such as stress-induced social avoidance can be de-coupled from circulating gonadal hormones in adults. Importantly stress-induced decreases in social approach are reversed with 4 weeks of chronic but not acute treatment with an antidepressant (Greenberg et al. 2014), as has been reported in male mice. The social interaction test has proved useful for assessing the possible utility of novel therapeutic approaches. For example, a single systemic dose of a brain-accessible oxytocin receptor (OTR) antagonist administered 30 min before a social interaction test was sufficient to restore social approach and reduce social vigilance in females that had been previously exposed to social defeat (Duque-Wilckens et al. 2018). In contrast, a short acting kappa opioid receptor (KOR) antagonist had no effect on behavior if administered before a social interaction test in stressed females (Williams et al. 2018). However, if KOR antagonists were administered immediately before each of three episodes of defeat, reductions in social approach and increases in social vigilance of females were blocked. These findings suggest that OTR antagonists might have unanticipated utility for reducing social anxiety whereas KOR antagonists might have more utility in prophylactic approaches to reduce the adverse impact of stressful experiences. Adult male California mice do not show a social anxiety phenotype following defeat in the social interaction test. However, pre-stress KOR antagonist treatment blocked defeat-induced sucrose anhedonia in both males and females (Williams et al. 2018). Site-specific manipulations suggest that OTR can have similar effects on social anxiety-related behaviors in both males and females.

For example, the BNST has been identified as a key brain region mediating the effects of social defeat on social approach and social vigilance (Duque-Wilckens et al. 2018, 2020). In stressed females, activation of OTR in the BNST is necessary for increased social vigilance while oxytocin infusions into the BNST of unstressed males or females are sufficient to induce social vigilance. Thus sex differences in the effects of defeat on social approach appear to be driven by differences in the activity oxytocin neurons. Females exposed to defeat 2 weeks prior to testing in the social interaction test have more oxytocin/c-fos colocalizations than control females whereas this difference is absent in males (Steinman et al. 2016). A key result is

that when oxytocin/c-fos colocalizations are examined within 1 h of a third episode of defeat, effects of stress are more robust in males than in females. When stressed males are tested in a social interaction test immediately after defeat exposure, the same combination of reduced social approach and increased social vigilance is observed (Duque-Wilckens et al. 2020). Thus, sex differences in the social interaction test appear to be largely based on the persistence of changes in social approach and vigilance. However, in more familiar environments (the home-cage), males and females show more similar responses to social defeat.

3.3 Context-Dependent Effects of Social Defeat

One of the first signs that effects of social defeat are context-dependent was observed in habituation-dishabituation tests. These tests are conducted in the familiar home-cage, in which mice are presented with diluted urine from unfamiliar same-sex conspecifics as a way to assess investigation of a social odor. Eight weeks after defeat, females spent significantly less time than controls investigating social odors (Trainor et al. 2011). Although stressed males showed more interest in social odors than stressed females, they spent significantly less time investigating these odors than control males. Similar results were observed in resident-intruder tests, where both males and females exhibited a conditioned defeat phenotype similar to male and female hamsters (Steinman et al. 2015). Stressed male and female California mice also exhibit reduced anogenital sniffing of intruders (which typically occurs before initiating aggression) and increased freezing behavior. Effects of stress also extend to sucrose preference, a widely used behavioral assay used to assess an anhedonia (loss of pleasure) phenotype. These tests are also conducted in the familiar home-cage. Both males and females exposed to social defeat show a reduced preference for sucrose (Williams et al. 2018). Together these results suggest that in males, the impact of stressful experiences is blunted in novel environments. This hypothesis is supported by conditioned place preference assays, which are conducted in novel testing arenas. Kappa opioid receptor agonists are generally aversive, and female California mice form a place aversion at lower doses than males (Robles et al. 2014; Laman-Maharg et al. 2017). There is no evidence for sex differences in the pharmacodynamics of KOR ligands (Laman-Maharg et al. 2018) and in general males are more sensitive to the aversive effects of KOR agonists than females (Russell et al. 2014; Chartoff and Mavrikaki 2015). Currently the basis for context-dependent effects of social defeat in California mice is unknown.

3.4 Male-Biased Effects of Stress on Cognitive Flexibility

Interestingly, one domain in which males are more strongly affected by stress than females is cognitive flexibility. When California mice were tested for spatial memory in a Barnes maze, social defeat had no effect on how quickly males and females learned to find an escape chamber (Laredo et al. 2015). However, when the location of the escape chamber was moved, stressed males had significantly longer path lengths to reach the escape chamber and made significantly more errors than controls. On the other hand, females were not affected by defeat stress during this reversal phase. A nearly identical pattern was observed in college students randomly assigned to undergo the Trier Social Stress Test (TSST) or a control condition (Shields et al. 2016). Men assigned to the TSST made more errors on reversal stages of the Wisconsin Card Sort task than controls whereas women were unaffected. Although California mice do not have strong spatial memory performance as other species of *Peromyscus* (Jašarević et al. 2012), the specific impact of defeat stress on reversal (but not acquisition) in males has been replicated in a 4-choice digging task that is less dependent on spatial memory (Wright and Trainor, unpublished). Previous work in rats reported that repeated restraint stress had stronger adverse effects on measures of cognitive flexibility in females than males (Grafe et al. 2017). This study used an operant task to assess reversal learning, so it is unclear whether task differences, forms of stress, or species differences contribute to the different results in California mice and rats.

3.5 Partner Loss Stress

An important alternative model for studying social stress is partner loss, which is associated with numerous adverse health outcomes in humans (Stroebe et al. 2007). California mice are one of the few monogamous species of rodents in which males and females form a pair-bond (Gubernick and Nordby 1993; Pultorak et al. 2015). Separation of a partner can impact the brain and behavior that go beyond social isolation. So far most work has been done in male California mice, but this set a groundwork for future work in females. For example, males that were isolated from a pair-bonded female had higher baseline corticosterone levels and slower healing of skin wounds (Glasper and DeVries 2005), similar to reports women experiencing the stress of a chronically ill spouse (Kiecolt-Glaser et al. 1991). To date, studies using females have yet to be published. In addition to assessing the physiological responses to isolation, it would be highly informative to know observed additional behavioral changes (i.e., signs of anhedonia, anxiety-like behaviors, increased social investigation following social deprivation, etc.).

3.6 Summary

California mice provide several options for studying the impact of social stress in ways that are translationally relevant for understanding behavioral phenotypes associated with anxiety and depression in women and men. Some phenotypes have proved remarkably robust, such as the social interaction test, which provides consistent results across hundreds of tests (Trainor et al. 2013). While effects of defeat in the social interaction test are sex-specific, other behavioral responses such as sucrose anhedonia and conditioned defeat are observed in both sexes. The relatively large size of this species (adults are 40 g) has also made this species amenable to site-specific pharmacological manipulations (Campi et al. 2014; Duque-Wilckens et al. 2016). The long life-span of California mice and prolonged period of adolescent development also makes this species conducive for the study of adolescent development (Wright et al. 2020). Although there has been progress in applying some modern neuroscience approaches to study the neural circuits impacted by stress (Duque-Wilckens et al. 2020), there are fewer molecular tools available compared to more conventional mouse and rat lines. As with hamsters, the growing availability of CRISPR based gene editing techniques may allow for the development of more tools for this species.

4 Prairie Voles and Mandarin Voles

The prairie vole (*Microtus ochrogaster*) is probably the best studied monogamous species of rodent, which is well known for its ability to form pair-bonds (Carter et al. 1995). Decades of work has identified neuroendocrine mechanisms underlying attachment within pairs (Young and Wang 2004) and parental behavior (Kenkel et al. 2017). One aspect of pair-bonding is selective aggression towards unfamiliar individuals in males (Winslow et al. 1993) and females (Bowler et al. 2002), which has been recently applied to study social defeat in females. Similar methods have also been adapted for Mandarin voles (*Microtus mandarinus*), a monogamous vole from Asia in which females are aggressive towards other females. In addition to social defeat methods, we will also briefly review studies that have examined partner loss as a form of social stress.

4.1 Social Defeat

For prairie voles, focal voles assigned to defeat undergo a combination of physical interaction with a same-sex resident (15 min) followed by a longer period of threat (45 min) in which the aggressive resident and focal vole are separated by a perforated barrier (Tickerhoof et al. 2019). Under this protocol, both males and females

vigorously attack intruders, although males attack more frequently than females. Social defeat results in an acute increase in corticosterone levels in female prairie voles (Smith et al. 2013). One week after defeat, both males and females exhibit reduced social approach towards an unfamiliar stimulus vole in a three-chambered test. Stressed males and females also show an anxiogenic phenotype in the elevated plus maze. No differences were observed in a sucrose preference test. These results show the prairie vole has strong potential for comparing social stress-related phenotypes in males and females.

Studies in Mandarin voles use a longer stress protocol, consisting of 2 weeks of daily 10 min episodes of physical social defeat (Wang et al. 2018). After this period of physical interaction, the focal vole is separated from the aggressive resident by a perforated barrier. Females assigned to this defeat protocol show reduced social approach and increased freezing in a social interaction test. Anxiogenic phenotypes are also observed in stressed female Mandarin voles during the elevated plus maze (Wang et al. 2019). Although males and females have not been directly compared using this protocol, these social defeat methods have been used to model stress buffering behaviors in pair-bonded voles (Li et al. 2019). Both males and females that observed a pair-bonded partner exposed to social defeat showed increased allogrooming behavior, suggesting that similar to prairie voles, males and females are highly sensitive to social stress. Together, these findings in prairie voles and Mandarin voles suggest that both species will be very useful for studying the neural circuits impacted by social defeat stress.

4.2 Partner Loss Stress

The loss of a pair-bonded partner is also an important form of stressor that can induce strong behavioral and neuroendocrine effects related to depression and anxiety. When males or females were separated from a pair-bonded mate, this induced passive immobility responses in the forced swim test and increased plasma adrenocorticotropic hormone and corticosterone levels in both sexes (Bosch et al. 2009; McNeal et al. 2014). A follow-up study showed that isolated prairie voles had greater corticosterone reactivity to a stressor following isolation from a mate (Grippo et al. 2020). In females, environmental enrichment (running wheel and other items) attenuated the behavioral effects of partner separation (Normann et al. 2018). Many of the behavioral effects of partner loss resemble the effects of social isolation in non-pair bonded prairie voles (Pizzuto and Getz 1998; Grippo et al. 2007, 2008; Ruscio et al. 2007, 2009; Pournajafi-Nazarloo et al. 2013).

4.3 Summary

Like hamsters and California mice, prairie voles and Mandarin voles can be studied to determine the impact of intra-female aggressive interactions on behavior and brain function. Although the neural circuitry affected by social defeat is only just beginning to be studied, decades of work on the neural mechanisms of pair-bonding in prairie voles provides a strong foundation for neural circuits of interest and methods for studying behavior in this unique species. In addition, the ability to study partner loss in prairie voles and Mandarin voles provides another important line of inquiry to understand how a different form of social stress affects depression and anxiety-related behaviors and corresponding neural circuits. Although currently there are few genetic tools available for voles, this is starting to change. New knockout (Horie et al. 2019) and knockin (Horie et al. 2020) prairie vole lines have been created using the CRISPR/Cas9 system, which demonstrates the feasibility of applying this approach to different rodent species (Donaldson and Manoli 2020). The ability to create voles with promoter-specific *Cre* recombinase yields the ability to target cell-type specific populations of neurons in a manner that previously was possible only in more conventional mouse and rat lines. In addition, advanced neuroscience techniques such as 1-photon in vivo calcium imaging have been adapted for use in prairie voles (Scribner et al. 2020), which allows for the measurement of neural activity in individual neurons. The development of these tools suggests that prairie voles will be an important model species for studying the impact of social stress in females.

Up to this point, the species reviewed are all ones in which intra-female is readily induced in laboratory settings. However, the majority of neuroscience tools have been developed for domesticated mouse and rat lines. In these species, intra-female aggression is low or absent in standard laboratory aggression tests. The need to study the impact of social stress in females has led to the development of some creative new approaches for studying females in these species.

5 Domestic Mice

Social defeat experiments using different transgenic lines of male C57BL/6J mice have proved to be a powerful tool for identifying circuits and molecular pathways related to depression and anxiety-related behaviors. A widely used protocol in mice (Golden et al. 2011) is based on work from Kudryavtseva and colleagues (Kudryavtseva et al. 1991; Avgustinovich et al. 1997) and involves 10 consecutive days of brief physical interactions with an aggressive resident. These interactions are followed by a period of sensory contact, in which focal mice are separated from aggressive residents by a perforated plexiglass barrier. During this time, residents often make aggressive threats towards focal mice. About half of male mice exposed to social defeat will show reduced social approach in a social interaction test (Krishnan et al. 2007). These mice are usually referred to as “susceptible,” and

this phenotype can be reversed by chronic but not acute antidepressant treatment (Berton et al. 2006). Interestingly, about half of males exposed to social defeat do not show a reduction in social approach and these mice are often referred to as "resilient." This term is something of a misnomer, as it implies that these mice have "recovered quickly" from a bad experience. In fact, when tested in other behavioral contexts like an elevated plus maze (Krishnan et al. 2007) or fear extinction (Meduri et al. 2013), strong effects of stress are observed. We will refer to this phenotype as "unsusceptible" to refer to the lack of phenotype in the social interaction test with the understanding that these mice still exhibit important stress-induced behavioral phenotypes.

Adapting social defeat methods to female mice has been challenging. In naturalistic contexts, male *Mus* typically defend territories from other males while females generally move between territories (Crowcroft 1955). Overt aggressive behaviors used by males to defend territories are largely absent in females (Scott 1966), at least under standard laboratory conditions. These aspects of *Mus* social organization have formed the main challenges to studying social stress in females. To overcome these barriers, three general strategies have emerged: (1) create behavioral contexts in which males will attack females, (2) construct paradigms in which females observe social defeat occurring among males, and (3) produce behavioral contexts in which females will attack females.

5.1 Male Aggression Towards Females

A chemogenetic approach uses designer receptors exclusively activated by designer drugs (DREADD) to enhance neural activity within circuits controlling aggression in male mice (Takahashi et al. 2017). To accomplish this, a virus expressing an excitatory DREADD was infused into the ventrolateral subdivision of the ventromedial hypothalamus (VMHvl). A systemic injection of clozapine-N-oxide (CNO) is then used to activate the VMHvl to robustly increase aggression towards both male and female intruders (Lin et al. 2011). This effect is mediated primarily by activation of neurons expressing estrogen receptor α (ERα) (Lee et al. 2014), and males attack females more readily when these neurons are selectively activated. When a standard protocol of 10 days of social defeat plus sensory contact was used, effects of defeat on social interaction behavior in females were surprisingly modest. Less than 20% of females showed a susceptible phenotype marked by reduced social approach to an unfamiliar female target mouse. In males, usually about 60% of mice show reduced social approach (Krishnan et al. 2007). The weaker effect in females could be due to the relatively transient nature of CNO activation of the Gq-DREADD in the VMHvl. Indeed, during the later phases of the sensory contact period, males did not make aggressive threats towards females across the barrier as is typically observed for male intruders. Thus, sensory contact between females and resident males might result in some kind of extinction learning. Indeed, social defeat of females by males without the sensory contact produced more robust decreases in

social approach. Similar to California mice, no effects of estrous cycle were observed on behavior in the social interaction test.

A shortened version of this social defeat protocol (only 3 days of social defeat) also induced significant decreases in social approach in females but not males (Issler et al. 2020), similar to typical results in California mice. This protocol was used to show that overexpression of the microRNA transcript LINC00473 in the medial prefrontal cortex (which is downregulated in women diagnosed with depression) blunts the effects of defeat stress on social approach in females. Another study showed that chemogenetic activation of ERα neurons in VMHvl can induce male aggression even when this mouse is introduced into the home-cage of female mice. A 6-day defeat protocol induced robust decreases in social approach as well as anxiety phenotypes in the elevated plus maze (Yin et al. 2019). Thus, it appears that the key to successful chemogenetic-assisted social defeat protocols for females is the elimination of the sensory contact phase rather than altering the number of episodes of social defeat. Chemogenetic activation of ERα neurons within VMHvl in female mice can also increase aggression towards female intruders in about 60% of tests (Hashikawa et al. 2017). This suggests that future refinements could produce a protocol based on female–female aggressive interactions.

A second general approach takes advantage of the role of olfactory cues to promoting aggression in rodents. Aggressive behavior is typically preceded by anogenital sniffing, during which the detection of male pheromones activates neural circuits driving aggression (Hashikawa et al. 2016). Collecting urine from a male CD-1 mouse and applying a sample of it to the base of the tail of a female C57BL/6J can induce aggression from male CD-1 in about 60% of tests (Harris et al. 2018). This approach was used in a 10-day social defeat protocol using sensory contact. After excluding stressed females that experienced fewer than 4 days of aggressive attacks over the 10-day protocol (23% of females), stressed females exhibited reduced social approach. When these females were divided into susceptible and non-susceptible females, susceptible females also exhibited reduced sucrose preferences. Estrous cycles were unaffected by social defeat. The male urine and chemogenetic methods rely on manipulations that strongly activate circuits for male–male aggression. However, these are not the only approaches for generating male–female aggression.

A third general approach is based on the observation that extremely aggressive male mice will often indiscriminately attack males or females. The introduction of focal C57BL/6J male *and* female mice into the home-cage of an aggressive CD-1 mouse causes the CD-1 resident to robustly attack the male intruder (Yohn et al. 2019). The CD-1 resident also attacks the female intruder, although significantly less (and with longer latency) than the male intruder. Intriguingly, CD-1s attack females throughout the estrous cycle, although rates are highest during proestrus and metestrus. Episodes of social defeat are conducted over a 10-day period with different CD-1s. During the sensory contact period, either the male or the female C57BL/6J intruder was cohoused with the aggressive CD-1. The cages used permitted only one cage divider, and co-housing male and female focal mice could cause a confound due to sexual experience. Thus on half of the days the focal male experienced

sensory contact with the familiar aggressive CD-1 while the female was housed with a novel CD-1 mouse. On alternating days the female was housed with the familiar CD-1 and the male housed with the unfamiliar CD-1. Thus each focal mouse experienced a total of 10 days of physical defeat with the 10 days of sensory contact (5 days spent with a familiar aggressor and 5 with an unfamiliar CD-1). About 70% of females exposed this social defeat regimen showed reduced social approach compared to controls. These females also showed anxiogenic phenotypes in the elevated plus maze and novelty-suppressed feeding test as well as sucrose anhedonia. Males exposed to this stress paradigm showed largely equivalent behavioral responses as females in all behavioral assays. Even though females were exposed to lower levels of physical aggression than males, robust behavioral phenotypes were observed. This is consistent with observations in California mice, where behavioral phenotypes were not strongly associated with the amount of aggression in individual episodes of defeat (Trainor et al. 2013).

5.2 Witness Defeat

The protocols reviewed above all rely on physical interactions between aggressive mice and focal mice, but mice show altered physiological responses when living with aggressive cagemates – even if they are not directly attacked (Henley et al. 1973). Building on these observations, an interesting discovery was that simply observing aggressive interactions can induce anxiety- and depression-like behavioral responses (Sial et al. 2016; Warren et al. 2020). Male C57BL/6J mice that observe other male C57BL/6J mice exposed to an aggressive male CD-1 mouse show similar increases in corticosterone both acutely and chronically (Warren et al. 2013). In fish (Oliveira et al. 2001) and humans (Bernhardt et al. 1998), observing competitions has also shown an increase in testosterone levels, a response that often occurs in individuals that win competitions (Marler and Trainor 2020). An important application of the witness defeat protocol was the demonstration of its utility in female mice (Iñiguez et al. 2018). One day after a female C57BL/6J observes social defeat of another male, corticosterone levels are significantly elevated. During this time, social approach and sucrose preferences are also reduced compared to control females that were handled but did not observe aggressive interactions. Female C57BL/6J mice exposed to witness defeat also show stronger increases in social vigilance than males (Duque-Wilckens et al. 2020). These phenotypes were reversed by acute treatment with low-dose ketamine or the anxiolytic chlordiazepoxide, illustrating pharmacological validity of this approach. Similar to California mice exposed to social defeat stress, witness defeat increased the number of oxytocin positive cells in the BNST but not the paraventricular nucleus of female C57BL/6J.

5.3 Female–Female Aggression

Previous work in mice demonstrated that lactating females will be aggressive towards female intruders, but this tendency is relatively brief (Svare and Gandelman 1973; Rosenson and Asheroff 1975). This is a major obstacle for implementing social defeat protocols. An alternative approach showed that when intact female Swiss Webster (CFW) mice were cohoused in pairs with intact male CFW mice, they reliably exhibited aggressive behaviors towards female C57BL/6J mice (Newman et al. 2019). Female aggressive behavior decreased steadily after females had pups but increased after females were repaired with castrated males. Similar to male C57BL/6J mice, females had increased corticosterone levels if exposed to either a single episode of defeat or after chronic exposure to 10 episodes of defeat. Females exposed to chronic defeat exhibited more defensive behaviors and reduced approach behaviors to a non-aggressive female intruder introduced to the home-cage. In stressed females, social approach was increased by low-dose ketamine treatment. Also, in the home-cage chronic social defeat impaired nest-building behavior, a motivated behavior that is stress sensitive (Otabi et al. 2016). A social interaction test using a large testing arena showed that females exposed to chronic defeat showed increased social vigilance, although curiously there was no effect on social approach. This observation is consistent with recent evidence indicating that neural mechanisms of social approach and social vigilance are distinct (Williams et al. 2020a). Similar to the other stress models reviewed above, estrous cycles did not appear to be impacted by stress and did not have robust effects on behavioral assays.

5.4 Summary

The methods reviewed above are exciting because they provide a mechanism for applying the powerful genetic tools developed for C57BL/6J to understand the molecular pathways and neural circuits contributing to stress-related behavioral phenotypes in females. While each approach has weaknesses, wide adoption of several of these methods will allow the field to rigorously identify stress-induced behavioral phenotypes and their associated neural mechanisms. A common strength of male-induced defeat of female mice is the generation of susceptible and unsusceptible phenotypes, similar to individual variation that has been identified in males. The ability to identify molecular- and circuit-based differences in these phenotypes has strong potential for understanding human resilience. However, common weaknesses are questionable ethological significance and the relative equivalency of phenotypes between males and females. While male aggression in rodents is rarely directed towards females in naturalistic contexts, these interactions clearly induce robust phenotypes. The introduction of new female intra-sexual aggression methods was an important methodological development (Newman et al. 2019) that has great potential. In the future, it will be interesting to assess

whether there are subtle differences between intra-sexual aggression versus inter-sexual aggression that might affect behavioral phenotypes or underlying neurobiological phenotypes. Regardless, these new behavioral models for transgenic mice will allow better use of molecular tools to study neural circuits of depression and anxiety-related behaviors.

6 Domestic Rats

As in mice, social defeat in male rats has proven to be a robust approach for inducing behavioral and neurobiological phenotypes related to depression and anxiety (Tidey and Miczek 1996; Wood et al. 2010). Most of the challenges faced by mouse researchers in adapting social stress protocols to females apply to rats as well. Two main approaches have been evaluated so far; lactating dams and witness defeat. In addition to these relatively new methods, there is a strong literature examining the effects of social instability stress during adolescence (McCormick et al. 2005; Hodges et al. 2018). In this approach, cagemates of developing rats are regularly switched, which creates an unstable social environment that has long-lasting effects on social behavior and brain function in males and females. These studies are reviewed in another chapter of this volume (McCormick 2021).

6.1 Lactating Dams

Lactating rat dams can be induced to exhibit aggression towards female intruders, with the peak aggression levels occurring during postnatal days 3–12 (Erskine et al. 1978). This approach has been used to examine effects of stress on anxiety and depression-related behaviors as well as drugs of abuse. In one study, female Wistar rats were exposed to a single episode of defeat by a lactating dam and then tested in a social interaction test 2 h later (Lukas and Neumann 2014). Social defeat did not reduce social approach to unfamiliar rats or a familiar cagemate, although there was a slight reduction in social approach if the same lactating dam was used as a stimulus rat. It is interesting that defeat does not induce robust decreases in social approach at this time point because in male mice (Bruchas et al. 2011) and California mice (Duque-Wilckens et al. 2020), social defeat can reduce social approach on this relatively short time scale. Future studies could examine whether multiple episodes of defeat might induce a more robust effect on social approach in female rats. It could also be informative to examine behavior several days after the last episode of defeat, as effects of defeat on social approach in California mice are stronger several weeks after the last episode of defeat compared to 1 day after (Trainor et al. 2011). Interestingly intracerebroventricular infusion of oxytocin in rats did not restore social approach in this condition, consistent with the hypothesis that oxytocin can reduce social approach in aversive contexts (Steinman et al. 2019).

Seven episodes of social defeat did not affect passive floating behavior by adult female Sprague-Dawley rats in a forced swim test conducted 2 days or 1 month after the last episode of defeat (Ver Hoeve et al. 2013). A different protocol alternated episodes of social defeat with restraint stress over a 12-day period (Bourke and Neigh 2011). This regimen decreased latency to engage in passive floating in the forced swim test and reduced sucrose preference in both adult and adolescent females. Both social defeat protocols induced defensive behaviors in focal females such as upright posture and boxing, so it's unclear why social defeat alone is insufficient to induce depression-related behaviors or passive coping responses in females. A procedure consisting of 3 weeks of daily aggressive encounters was used in which focal female rats were introduced into the home-cage of an aggressive dam (Shimamoto et al. 2011). Episodes of aggression occurred twice per day. After 1 week of stress, stressed females showed a significant reduction in saccharin preference. The prolonged stress exposure also disrupted estrous cycles. Stress also blunted dopamine and serotonin release in the NAc in response to cocaine. In contrast, other studies using fewer episodes of defeat show that stressed female rats self-administer cocaine at higher rates (Haney et al. 1995) and enhanced dopamine release in the NAc following a cocaine challenge (Holly et al. 2012).

6.2 Witness Defeat

A challenge for implementing social defeat with lactating dams is the need to maintain breeding pairs as aggression levels that occurs shift as pups grow older. An alternative approach includes witness defeat, in which Sprague-Dawley female rats observe another male exposed to defeat on 5 consecutive days (Finnell et al. 2018). During episodes of defeat females threw bedding at the partition separating the female from the males, similar to defensive treading behavior reported in male rats (Cromwell and Berridge 1994). In tests conducted 3–4 days after the last episode of defeat, stressed females had decreased sucrose preference and increased passive floating behavior in a forced swim test. However, the effects of stress on these behaviors were blunted in ovariectomized females, even though there were no differences in behavior across the estrous cycle.

It's unclear why this witness protocol induced behavioral responses in the forced swim test whereas previous studies using lactating dams as aggressors did not (Ver Hoeve et al. 2013). Both studies included a delay between defeat exposure and behavior testing, although the lactating dam study waited 1 month. Although social defeat-induced decreases in social approach behaviors have been observed to last for 8 weeks (Trainor et al. 2011), it's possible that passive coping strategies may recover more quickly. Further study is needed to assess the timeline of behavioral phenotypes for lactating dam-induced stress and witness defeat. It would also be interesting to assess the impact of these stress models on social approach or vigilance.

6.3 Summary

To date, the strongest effects of female–female defeat have been on reward-related behaviors such as cocaine self-administration or saccharin preference. While the effects of female–female social defeat on social behavior are not as strong as male–male social defeat, there is still potential to examine longer term effects of stress. Experimenting with female aggression in sexually experienced females (similar to new methods in mice) could be worth investigating to reduce the constant need for lactating dams, which are only aggressive for a short period of time. New witness defeat methods are also an attractive alternative for inducing robust physiological and neurobiological responses to stress. The use of CRISPR has led to rapid growth in the availability of new transgenic rat lines (Bäck et al. 2019), which should facilitate the types of cell-type specific manipulations that are currently available in mice.

7 Conclusions

An important question moving forward is how some of the methods will shed light on underlying mechanisms for sex differences in stress-related psychiatric disorders. For many of the new models reviewed above, investigators focused on establishing novel methods in females and did not directly compare males and females. A few cases have directly compared males and females. In some cases, behavioral phenotypes were similar such as in mice (Yohn et al. 2019) or prairie voles (Tickerhoof et al. 2019). In other cases, such as Syrian hamsters and California mice, the effects of social defeat in males and females are context-specific. In light of the increased prevalence of stress-related mental illnesses in women compared to men, it might be expected that, for at least some behavioral variables, there could be sex differences. A challenge for comparing results across species is that different methodologies are used. Although several studies have compared one versus multiple episodes of social defeat, other parameters such as sensory contact likely play an important role in determining behavioral phenotypes. Systematic evaluation of these parameters across species could provide key insights in understanding the mechanisms of behavioral phenotypes. For example, while a typical chronic mild stress protocol induced depressive-like behaviors in both males and females, an abbreviated subchronic mild stress protocol has stronger effects in females than males (Hodes et al. 2015). It is important to note that studying the same phenotype in both males and females is intrinsically valuable because different neurobiological mechanisms can produce a similar phenotype in males and females (De Vries and Boyle 1998; Shansky 2018). Overall, these innovative methodologies provide a path for investigators to examine how stress alters molecular and neurobiological pathways regulating stress-sensitive behaviors in females.

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