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Resilience to the effects of social stress: Evidence from clinical and preclinical studies on the role of coping strategies

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ABSTRACT

The most common form of stress encountered by people stems from one's social environment and is perceived as more intense than other types of stressors. One feature that may be related to differential resilience or vulnerability to stress is the type of strategy used to cope with the stressor, either active or passive coping. This review focuses on models of social stress in which individual differences in coping strategies produce resilience or vulnerability to the effects of stress. Neurobiological mechanisms underlying these individual differences are discussed. Overall, the literature suggests that there are multiple neural mechanisms that underlie individual differences in stress-induced resilience and vulnerability. How these mechanisms interact with one another to produce a resilient or vulnerable phenotype is not understood and such mechanisms have been poorly studied in females and in early developmental periods. Finally, we propose that resilience may be stress context specific and resilience phenotypes may need to be fine-tuned to suit a shifting environment.

1. Introduction

The most common form of stress encountered by people stems from one's social environment and is perceived as more intense than other types of stressors (Almeida, 2005). Socially stressful events such as bullying, loss of a loved one, and psychological abuse are well documented to contribute to psychopathology (Kendler et al., 1999; Kessler, 1997; Bjorkqvist, 2001). In fact, stress exposure is an independent risk factor for psychiatric disorders such as depression, anxiety and posttraumatic stress disorder (PTSD) (Kendler et al., 1999; Kessler, 1997; Javidi and Yadollahie, 2012). However the pathogenic potential of a stressor does not solely depend on the severity of the stress exposure as evidenced by the great individual variability in the consequences of exposure to stressful events. Indeed, a recent study indicates that among older US veterans who have been exposed to a high number of lifetime traumas, about 70% are resilient in later life (Pietrzak and Cook, 2013). One feature that may be related to differential susceptibility to stress is the type of strategy used to cope with the stressor, either active or passive coping (Veenema et al., 2003). Active coping is defined as a behavioral response people engage in that uses one's own resources to minimize the physical, psychological or social harm of a situation (Folkman and Lazarus, 1980) and is related to resiliency to stress (Southwick et al., 2005). In humans, developing social support and friendships (Kral et al., 2014; Yi et al., 2005) as well as having secure relationships reduces suicidality in veterans of Operation Enduring Freedom and Operation Iraqi Freedom (Youssef et al., 2013), and is essential to establishing resilience. Furthermore, characteristics of active coping that reduce stress and symptoms of mental illness include the following: creating a sense of coherence in their lives (Matsushita et al., 2014) or in the community (Hall et al., 2014), exercising self-control (Moses, 2014), developing a strong sense of identity including professional identity for workplace resilience (Hunter and Warren, 2014), maintaining a realistic perception of threat (Karstoft et al., 2013), possessing optimism (McGarry et al., 2013; Boyson et al., 2014), having a sense of purpose (Pietrzak and Cook, 2013), and the use of problem-focused coping (Yi et al., 2005). However not all coping strategies are adaptive; passive coping is characterized by feelings of helplessness, relying on others for stress resolution and is associated with vulnerability to psychopathology (Zeidner and Norman, 1995; Folkman and Lazarus, 1980; Billings and Moos, 1984). Consistent with this view, vulnerable individuals use

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passive coping strategies such as avoidance and blaming others (Yi et al., 2005). Therefore, the impact of a stressor on an individual's psychological well-being depends to a considerable extent on the strategy used to cope with the stressful life event.

2. Focus of this review

Resilience can be defined as positive adaptation, or the ability to maintain or regain mental health, despite experiencing adversity and challenges (Herrman et al., 2011; Karatsoreos and McEwen, 2013). In order to understand the biological basis of how some individuals are resilient to social stress and how others are vulnerable, we will focus on studies in which variations in the impact of stress are observed. That is, the focus is on studies in which subgroups of individuals defined as vulnerable or resilient emerge following exposure to the same stressor and not on studies that examine mechanisms that modify the impact of social stress homogenously in all subjects. This is because not all mechanisms that uniformly reduce the impact of stress necessarily underlie resilience. They may underlie resilience or they may not, but focusing on studies in which subpopulations emerge will allow the determination of those specific mechanisms demonstrated to underlie resilience and/or vulnerability. Further, because of the robust impact that stress has on mental health, we have a particular focus on those studies in which measures related to psychopathology are assessed. Furthermore, in clinical literature, varying coping strategies have been associated with differences in susceptibility to stress-related pathology. As such, we also focus on the role that various coping strategies may play in vulnerability to psychosocial stress exposure. Finally, there are a substantial number of studies examining epigenetic mechanisms underlying resilience to social stress but these are covered elsewhere in this issue and excellent recent reviews have been published (Wu et al., 2013; Griffiths and Hunter., 2014; Nestler, 2014). Therefore, the impetus for this review is to highlight how mechanisms linked to either a passive or active coping strategy in the face of chronic psychosocial stress may underlie the pathogenesis of stress vulnerability and resiliency.

3. The resident-intruder paradigm of social stress

The resident-intruder paradigm is an ethologically relevant animal model of social stress (Miczek, 1979) that has proven useful for identifying mechanisms mediating resilience or vulnerability to stress-related consequences (Wood et al., 2010, 2013a; Koolhaas et al., 2007; Krishnan et al., 2007; Berube et al., 2013). This model is commonly employed using rodents (rats, mice, hamsters) or tree shrews and involves subjecting a male “intruder” to aggressive threats from a larger, unfamiliar male “resident” by placing it in the resident's home cage for a period consisting of anywhere from 5 to 60 min (Krishnan et al., 2007; Bhatnagar and Vining, 2003; Wood et al., 2010; Miczek, 1979; Sgoifo et al., 1996; Buwalda et al., 1999). The acute response to social defeat (minutes to hours) results in robust sympathetic activation eliciting 30 times the number of arrhythmias as compared to other non-social experimental stressors such as foot shock or restraint (Sgoifo et al., 1999). Social stress also produces vagal withdrawal, increased blood pressure, elevated plasma catecholamines, hyperthermia, and increased activation of the hypothalamic–pituitary–adrenal (HPA) axis (Wood et al., 2010; Sgoifo et al., 1999; Tornatzky and Miczek, 1994, 1993; Bhatnagar et al., 2006). These acute physiologic stress responses are comparable to those reported in response to an experimental model of psychosocial stress in humans. For example, the Trier Social Stress Test is designed to exploit the reactivity of the stress response to socially challenging situations in humans and produces robust activation of the HPA axis and the sympathetic nervous system (Hellhammer and Schubert, 2012; Kirschbaum et al., 1993). In both humans and animals, these acute responses are adaptive in helping the individual cope with the stressor. However, if these stress responses are unabated in the face of chronic stress as may occur under conditions of inefficient stress coping, this can lead to pathological changes promoting psychiatric disorders such as depression, generalized anxiety and post-traumatic stress disorder.

4. Coping influences individual differences in reactivity to, and consequences of, social stress in the resident-intruder and visible burrow models

It is generally considered that two coping response patterns are distinguishable in response to social stress (Koolhaas et al., 1999). One is considered the active (or proactive) response and is characterized by territorial aggression and control, as was originally described by Walter Cannon (Cannon, 1915). The second category of stress coping response is defined as passive (or reactive) and is characterized by immobility and low levels of aggression (Engel and Schmale, 1972). These two coping strategies have distinct and opposing sets of behavioral characteristics (reviewed in Koolhaas et al. (1999)). Coping styles have now been identified in a range of species from fish to rodents and pigs to humans and non-human primates (reviewed in Koolhaas et al. (1999)) and are considered to be trait characteristics that are stable over time and across situations (Koolhaas et al., 2007). In addition to the distinct behavioral characteristics displayed by the active and passive coping strategies, these strategies are also characterized by differences in physiological and neuroendocrine endpoints (reviewed in Koolhaas et al. (1999)). Freezing, a characteristic behavior of passive coping, is accompanied by low plasma norepinephrine and high plasma corticosterone levels. Furthermore, passive coping is associated with high HPA axis reactivity (Korte et al., 1992). In contrast, active coping is distinguished by low HPA axis reactivity and high sympathetic reactivity to stressful situations (Fokkema et al., 1995). Based on these diverse physiological responses to stress in actively versus passively coping individuals, under conditions of chronic stress when the coping response is not adequate to mitigate the impact of stress on the body, negative stress-induced physiological and psychological consequences may ensue. The majority of the studies discussed below are in the context of exposure to psychosocial stress in rodents under conditions in which death is not imminent. It is important to note that whether a specific coping strategy is adaptive (i.e. resulting in decreased impact of stress on the body) is dependent on the environment and type of stress. For example, the studies discussed below indicate that passive coping (i.e. submissive, immobile responses) is maladaptive under conditions of repeated exposure to brief social stress. However, under conditions where a weaker organism is confronted with a life-threatening situation involving a predator, passive immobility rather than fighting and struggling will likely increase the chance of survival. Therefore passive immobility may be considered adaptive under conditions where there is no possibility of escaping or winning the fight (Bracha et al., 2004). Therefore the concept of a particular coping strategy leading to healthy adaption must be a fluid concept; a specific coping strategy may be considered adaptive in one context and maladaptive in another.

Two experimental animal models have been particularly important in understanding the impact of coping strategies on the physiological and behavioral consequences of social stress, the resident-intruder paradigm originally developed by Miczek (1979) and the visible burrow system (VBS) developed by Blanchard, Blanchard, Sakai and colleagues (Blanchard et al., 2011; Tamashiro et al., 2005). Other models of social stress have been developed,

such as the social instability model, and these have increased our understanding of how social stress changes physiology and behavior. However, to our knowledge, there are no reports of individual differences in response to social instability, therefore these other models are not discussed here.

The resident-intruder model of social defeat has proven useful for studying the influence of coping responses on vulnerability to stress-related consequences relevant to human pathologies (Wood et al., 2010, 2013a). Rodents exhibit varying coping strategies in response to social defeat, resulting in individual differences in their reactivity and consequences to social stress. In an outbred population of Sprague Dawley rats we previously reported two distinct phenotypic responses to repeated social defeat using the resident-intruder paradigm (Wood et al., 2010). One population exhibited passive coping behaviors and assumed a supine, submissive posture within a short latency (termed SL). The other phenotype developed proactive coping behaviors as early as the third exposure to social defeat, indicated by upright postures and a resistance to display the supine defeat posture, resulting in a longer latency (LL). The passive SL phenotype was characterized by exaggerated HPA reactivity during repeated social defeat as compared with the proactive LL rats, and an impaired HPA response to a novel stressor (Wood et al., 2010). In support of our findings, Walker et al. (2009) compared the effect of a single social defeat on the neuroendocrine response and found a negative association between defensive guarding behaviors during defeat and corticosterone release.

In another type of social stress model in rodents, the VBS, dominance–subordination relationships are established within the first several days and are stable over the lifespan of the group (Blanchard et al., 1988). Distinct from the episodic nature of many social defeat paradigms where an intruder is placed into the home territory of a novel aggressive conspecific on each day of the stressor, VBS is a continuous stressor that consists of mixed-sex rat groups maintained over several weeks (Blanchard et al., 1995). One dominant rat emerges in each group and is characterized by offensive or aggressive attacks. The remaining subordinate rats are characterized by severe weight loss. In fact, this stress is so severe in submissive animals that if they are not periodically removed from the VBS this stressor can result in death (Blanchard et al., 1995). Like the social defeat paradigm, rats subjected to VBS exhibit evidence of endocrine dysfunction such as adrenal gland hypertrophy and elevated circulating corticosterone (Blanchard et al., 1995). Dysfunction within the HPA axis is reported in some depressed patients (Nemeroff et al., 1984). Therefore, passive coping during social stress exposure in the resident-intruder paradigm and VBS promotes sensitivity to HPA dysfunction that is also observed in depressed patients.

In addition to physiological repercussions, social defeat and VBS stress engender behavioral disturbances that are strikingly isomorphic to symptoms of clinical depression. After exposure to social defeat using the resident-intruder paradigm, rats that adopted a passive coping response (SL rats) in the face of repeated brief exposure to social stress exhibited enhanced susceptibility to displaying depressive-like behaviors, as indicated by increased immobility in the Porsolt forced swim test (Wood et al., 2010), and decreased sucrose preference as well as increased social anxiety (unpublished findings), while the LL phenotype remained generally resistant to these changes. The impact of coping strategies and dominance/submissive roles on stress-related pathology has also been demonstrated following social stress in tree shrews. In nature, when tree shrews fight, the subordinated animal must leave the territory. However seminal studies by Von Holst (1972) forced the subjugated animal to be in constant visual and olfactory contact with the victor. Under these conditions, the subordinate animal spent the majority of the day lying motionless in the corner of the cage and many of them eventually died. In a more recent, related model of social stress in tree shrews, subordinate animals exhibit reductions in general motor activity, grooming, and food and water intake (Kramer et al., 1999). Similarly, subordinate rats in the VBS also demonstrate reduced food intake and exaggerated weight loss, decreased sexual and social behaviors, and altered sleep cycles (Blanchard and Blanchard, 1989). Behavioral disturbances and dysfunction within the HPA axis are reported as persistent outcomes and mimic maladaptive changes seen in people with psychiatric diseases (Wood et al., 2010; Bhatnagar and Vining, 2003; Buwalda et al., 1999; Stefanski, 1998). These studies emphasize how a variation in coping response influences the pathogenic potential of social stress.

5. Sex and gender differences

Gender differences in both prevalence and symptomatology of affective disorders are well-established (Garber, 2006). Women display up to two-fold higher rates of depression, anxiety and seasonal affective disorders than men (Kessler et al., 1994). Higher suicide rates are found in men while increased numbers of suicide attempts are found in women (Hawton, 2000). Depressed women are also more likely to display atypical symptoms than men, including weight gain, increased appetite and increased sleep (Rappaport et al., 1995).

Considerable sex differences exist in the social relationships of adolescent humans (described more below) and adult humans. Current theory posits that adult females exhibit affiliative behavior (a “tend and befriend” response) whereas males exhibit more of a fight or flight response to stress (Rose and Rudolph, 2006). Oxytocin is thought to be important in female affiliative behavior whereas testosterone or vasopressin might be more important for male social behaviors. However, social support and the presence of strong social relationships play an important role in both men and women. In both genders, social support and social experiences are associated with reduced impact of stress on the body, as measured by HPA activity, sympathetic activity and metabolism (Seeman et al., 2002).

At this time, there are a number of challenges to our understanding of resilience and vulnerability to stress in females. There is a relative lack of social stress models in which individual differences in females have been observed. Little is known about whether the same kinds of behaviors define resilience and vulnerability in stressed females as they do in males. Finally, whether the same mechanisms influence vulnerability and resilience in females as they do in males is not known. In terms of mechanisms, a good place to start would be to look at the individual differences in the mechanisms that underlie the sex difference in responses to stress. This includes work demonstrating that gonadal hormones regulate HPA responses to stress (Goel et al., 2014) and that alterations in trafficking and internalization of the CRF_1 receptor on locus coeruleus neurons of females may promote activity of the locus coeruleus-norepinephrine system (Bangasser et al., 2013). This type of work will be crucial in advancing our understanding of resilience and vulnerability in female individuals.

6. Coping behaviors in adolescence

Peer relationships are the primary source of life stressors in adolescent boys and girls though there are striking sex differences (Hankin et al., 2007). Adolescent girls report higher levels of stress associated with their friendships, report more negative life events and experience more distress when such negative life events occur (Hankin et al., 2007). 17–23 year old females (adolescents/young adults) exhibit enhanced salivary cortisol responses to social rejection whereas males exhibit enhanced responses to challenges to their achievement (Stroud et al., 2002). These differences

between adolescent boys and girls are important because peer socialization is key to the development of normal social behavior later in life. Furthermore, the sex difference in rates of depression, in hypothalamic pituitary adrenal (HPA) responsivity to stress and anxiety-related behaviors emerges during adolescence.

In adolescents as in adults, there is a strong link between depression and stressful life events with a stressful life event often preceding an episode of depression (Hankin, 2006; Garber, 2006; Miller, 2007). The sex difference in rates of depression and in anxiety-related behaviors emerges during adolescence, around 14–15 years of age in humans (Eberhart et al., 2006) and about 50% of depressed adolescents exhibit major depression into adulthood (Miller, 2007). Furthermore, self-reports of anxious and depressive symptoms in early adolescence predict occurrence of major depression at later ages (Pine et al., 1999; Reinherz et al., 2000) suggesting that depressed mood in adolescence is a risk factor for the development of affective disorders in adults. It is well established that stress during adolescence produces a long-lasting impact on measures of mental health in both clinical and preclinical studies (Weintraub et al., 2010; Ver Hoeve et al., 2013; Hong et al., 2012; McCormick et al., 2007; Isgor et al., 2004) and that there are sex differences in the impact of social stressors like social isolation in adolescence (Hong et al., 2012). In addition, in humans, the active coping strategies that contribute to resilience during psychosocial stress exposure (discussed at the beginning of the manuscript) are also important in contributing to resilience in adolescence (Kral et al., 2014; Hall et al., 2014). Conversely, passive strategies in adolescents as indicated by disengagement or aggression are associated with greater severity of mental illness symptoms when challenged with the threat of social stigma (Moses, 2014). In the natural environment of rats, adolescents live in groups and exhibit higher levels of social behavior than either younger or older animals (Panksepp et al., 2007). Coping strategies during social defeat in rodents, as defined by the display of the defeat posture, do emerge during adolescence (Bingham et al., 2011). However, after they have emerged during this critical developmental period, little is known about the role of coping strategies in mediating resilience to social stress. Thus, this gap in our knowledge hinders our ability to understand resilience to stress in adolescence. Furthermore, because the impact of stressful events in adolescence and adolescents' ability to cope with these events influences responses to stress in adulthood, this gap also hinders our ability to fully understand the mechanisms that mediate resilience in adulthood. Finally, the long-term impact of stress during adolescence cannot be fully understood without considering that there may be tremendous change in the individual's environment from adolescence to adulthood. The impact of a specific kind of stress on brain plasticity during adolescence may be advantageous later on for the individual if the plasticity is suited to that environment. If the environment shifts, than the plasticity may produce an adverse impact (Daskalakis et al., 2014). This kind of mismatch from the adolescent to the adult environment may be a critical factor in determining whether an adult is resilient or vulnerable to stressors experienced earlier in life.

7. Sources of individual differences in response to social stress

a. *Circulating glucocorticoids*

In response to chronic social stress, a common finding is an elevation in morning corticosterone and increased adrenal weight (Tamashiro et al., 2005). Jacobson and colleagues have shown that variations in morning corticosterone concentrations in mice exposed to two weeks of social defeat are associated with markedly different behavioral phenotypes (Bowens et al., 2012). They observed that a subpopulation of defeated mice that did not exhibit this increase in morning corticosterone exhibited anhedonia in the sucrose preference test as well as anxiety type behaviors whereas mice with an elevated morning corticosterone were not different from control groups. Weeks after stress has terminated, corticosterone can be expected to return to normal, however Schmidt et al. (2010) identified a subset of mice that continued to exhibit high levels of morning corticosterone 5 weeks after 7 weeks of social instability. These mice were considered vulnerable. The possibility that AMPA receptors were involved in promoting this vulnerability was examined because of the link between stress-related psychiatric disorders and glutamate functions (Hashimoto, 2009; Bleakman et al., 2007). Vulnerable mice exhibited increased expression of the AMPA receptor subunits GlurR1 and R2 mRNA in the dentate gyrus and CA1, and elevated GluR2/GluR1 ratio indicating increased availability of the GluR2. The AMPA receptor potentiator LY452646 reversed the increased HPA activity. Furthermore, a polymorphism in the GluR1 gene conferred vulnerability to social stress suggesting, overall, that glutamate receptors are important in conferring vulnerability to stress as assessed by protracted HPA activation even after termination stress.

b. *Pre-existing differences*

Akil and colleagues adopted a model from Piazza et al. (1989) in which animals inherently exhibit either high or low responsivity to novelty seeking. When these high and low responders, respectively, are exposed to chronic social defeat, the high responders exhibit increased anxiety, social avoidance, and pro-depressive behavior compared to the low responder group (Duclot et al. 2011). In a related study, outbred rats that engaged in greater levels of novel environment exploration, burying during the defensive burying test, and guarding during social conflict displayed less evidence of conditioned fear to the social conflict arena (Walker et al., 2008). Thus, the impact of social defeat is partly determined by the inherent novelty seeking behavior of the individual. While these studies suggest that resilience may be a predisposition, studies from our group indicate that such resistance to social defeat stress may be an adaptation that occurs with repeated exposure to stress. For example, the behavioral reactivity (as indicated by the latency to submit to the aggressive resident) and HPA response to social stress are comparable upon the first exposure to social defeat in Sprague Dawley rats (Wood et al., 2010). However, upon subsequent exposures the resilient, active coping response emerges in LL defeated rats and is associated with adaptation within the HPA axis. This effect is delayed or absent in passive coping SL rats. Furthermore, stress-induced adaptations evident within the CRF system (discussed below) in the active coping LL rats are significantly different from the group of non-stressed controls, suggesting that these differences represent adaptations in response to social stress exposure, not pre-existing differences. This does not rule out that there are likely some pre-existing differences, but resilience and vulnerability to stress may be a dynamic combination of genetic and environmental differences impacted by stress-related adaptations.

Importantly, there are also genetic strain differences in the behavioral response to learning tasks and stress responsivity that have been extensively characterized by Crawley et al. (1997). For example they reported that C57BL/6 mice exhibit exceptional complex learning while BALB/c mice exhibit poor learning responses comparatively. In addition, BALB/c mice demonstrate increased anxiety-like behaviors compared with C57BL/6 mice in the light/dark test of anxiety. Differences in the response to social

defeat stress in different strains of mice have also been reported. Savignac et al. (2011) examined behavioral and physiological responses to 10 days of social defeat in BALB/c and C57BL/6 strains. The more sensitive BALB/c strain was overall more sensitive to the effects of social defeat, including impairments in social interaction and exhibiting spleen hypertrophy and thymus atrophy indicating that there is a genetic basis for sensitivity to social defeat.

c. *Prior environmental perturbations*

While social stress exposure is clearly documented to induce long lasting adverse adaptations in physiology and behavior, manipulations of environmental conditions can impact the consequences of social stress exposure. For example, individually housing rats following a single 60 min exposure to social stress exacerbates stress-induced decreases in body weight gain and increases in anxiety-like behavior. Furthermore, in this study HPA axis activity was also elevated in rats that were singly housed following the social defeat exposure, as compared with rats that were group housed (Ruis et al., 1999). Prior environmental enrichment can prevent some of the effects of social defeat in adult mice. Lehmann and Herkenham (2011) exposed adult mice to environmental enrichment followed by 10 days of social defeat. The defeated mice that lived in an enriched environment did not show the increased immobility in the FST and TST, the increased time spent in the dark in the light/dark test and decreased social interaction behaviors that were exhibited by defeated mice living in an impoverished or standard environment. Lesions of the infralimbic prefrontal cortex prevented these effects of environmental enrichment if the lesions occurred before the enrichment was provided suggesting that the infralimbic prefrontal cortex plays a critical role in the ability of environmental enrichment to produce resilience to stress.

8. Neurobiological substrates underlying stress susceptibility/resilience

Resilience in the face of chronic social stress is an active neurobiological process that has been linked to various brain regions and neurotransmitters/neuropeptides (Charney, 2004; Krishnan et al., 2007; Sajdyk et al., 2008; Berube et al., 2013). In fact, a comprehensive analysis of neuronal activation across the entire brain in hamsters exposed to social stress indicates that distinct brain regions are activated to varying degrees in dominant versus submissive animals (Kollack-Walker et al., 1997). The following sections of this review report evidence from clinical and preclinical social stress studies highlighting putative neural substrates of resilience or vulnerability to social stress.

a. *Corticotropin-releasing factor*

There are several stress-sensitive biological molecules that have pro-depressive or anxiogenic effects and are dysregulated following chronic stress in susceptible individuals. One potential biomarker is corticotropin-releasing factor (CRF). This neuropeptide is considered the “hallmark” of the stress response as it is the initiating hormone in the HPA axis (Vale et al., 1981). In extra-hypothalamic regions of the brain such as the amygdala, locus coeruleus (LC) and dorsal raphe CRF receptor activation is involved in stress-related emotionality and produces behavioral features of the stress response (Dunn and Swiergiel, 2008; Wood and Woods, 2007; Ayala et al., 2004; Valentino et al., 2009; Hammack et al., 2003; Heinrichs et al., 1992). Given CRF's pervasive influence, it plays a central role in the behavioral, neuroendocrine and cardiovascular limbs of the stress response.

Like many elements of the stress response CRF is capable of promoting healthy adaptation to stress (Vale et al., 1981), but when unabated it can lead to pathology. For example, transgenic mice engineered to over-express CRF in the brain are disposed to exhibiting a depressive- and anxiety-like phenotype (Bangasser et al., 2013; Vicentini et al., 2009). Furthermore, Elliott et al. (2010) demonstrated that chronic social stress in adult mice produced long-term demethylation of the CRF gene. Interestingly, demethylation was only observed in the subset of mice that displayed social avoidance as a consequence of social defeat. Using site-specific knockdown of CRF, the authors confirmed the role of methylation of the CRF gene in resilience to social stress. Moreover, social stress exposure impacts CRF levels and CRF receptor distribution and quantity in brain and pituitary (Wood et al., 2010; Wood et al., 2013a; Chaijale et al., 2013; Wood et al., 2009). In the VBS, male subordinate rats exhibited higher CRF mRNA expression in the central amygdala as compared with dominant rats and controls and a subset of the subordinate males had higher CRF mRNA expression in the PVN (Albeck et al., 1997). Furthermore, social stress using the resident intruder paradigm shifted CRF receptor signaling in the dorsal raphe from CRF_1 to CRF_2 in active coping, resilient rats while this adaptation was absent in passive coping rats (Wood et al., 2013b). Because the resilient active coping phenotype (LL rats) was characterized by CRF_1 receptor internalization, we treated rats with the centrally acting CRF_1 antagonist NBI-30775 (Wood et al., 2012). CRF_1 blockade shifted rats towards exhibiting the LL resilient phenotype; upright postures and defeat latencies were increased, behavioral despair in the forced swim test was inhibited, and neuroendocrine consequences of social defeat were prevented by NBI-30775 treatment (Wood et al., 2012). In humans, overproduction of central CRF as evidenced by increased CRF in cerebrospinal fluid has been identified in patients with anxiety disorders such as PTSD and depressive disorders (Nemeroff et al., 1984; Baker et al., 1999; Bremner et al., 1997). In post mortem depressed patients, specific changes in CRF within brain regions critical to the stress response and implicated in psychiatric disorders have also been documented. For example, increased CRF protein levels have been documented in the locus coeruleus and the paraventricular nucleus of the hypothalamus (Bissette et al., 2003; Austin et al., 2003; Raadsheer et al., 1994). Furthermore, CRF receptor mRNA down-regulation was reported in the frontal cortex of depressed patients and was thought to be a secondary consequence of exaggerated CRF release (Merali et al., 2004). Therefore, converging lines of evidence underscore the role of CRF in susceptibility to stress-related psychiatric disorders.

b. *Dopamine cell body regions and reward circuitry*

Considerable attention has been paid to the role of dopamine neurons in the VTA, a region involved in reward circuitry, in vulnerability and resilience to social defeat. In the studies discussed below, 10 days of defeat in mice produces a vulnerable subpopulation defined by social avoidance, anhedonia and depressive type behaviors whereas the other subpopulation doesn't exhibit these deficits, displaying resilience to social defeat. The social stress of defeat in mice is arguably a more intensive and aggressive situation than in rats so comparisons across species must be made carefully. The VTA is important because increased excitability of VTA neurons is observed in vulnerable mice *in vitro* and *in vivo* (Krishnan et al., 2007; Von Holst, 1972) and this is associated with increased brain-derived neural growth factor (BDNF) in the nucleus accumbens, a neurotrophin important for neuronal plasticity and capable of increasing dopamine release (Altar et al., 1992). In fact, intra-

nucleus accumbens infusions of BDNF increased susceptibility to social defeat (Krishnan et al., 2007). Importantly, increased activity of this VTA-nucleus accumbens pathway is associated with susceptibility in socially defeated mice. The idea that VTA excitability is associated with susceptibility was directly assessed more recently. In this study (Chaudhury et al. 2013), VTA neurons were optogenetically stimulated during subthreshold exposure to defeat that does not on its own produce behavioral deficits. Phasic stimulation of TH positive neurons in the VTA decreased social interactions and decreased sucrose preference in defeated mice, thereby producing a vulnerable phenotype. A similar finding was observed if VTA dopamine neurons were phasically stimulated during social interaction testing, mimicking the effects of repeated defeat. These effects were not seen in naïve mice in which VTA dopamine neurons were stimulated, suggesting that these effects require the presence of stress. Furthermore, resilient mice in which VTA dopamine neurons were stimulated showed reduced social interactions on a second test. Optogenetic stimulation of VTA neurons produced increased neuronal activity that was observed up to 12 h after optogenetic stimulation. These effects of VTA dopamine neuron stimulation were primarily due to stimulation of projections to the nucleus accumbens as stimulation of these projections could recapitulate the findings of VTA dopamine neuron stimulation. Together these findings showed that VTA dopamine neuron excitability is a primary source of vulnerability of socially defeated mice to anxiety- and depressive-like behaviors. In rats, although continuous exposure to social defeat was reported to produce significant anhedonia, BDNF levels were reduced in the VTA and spontaneous DA release and cocaine-induced DA release in the nucleus accumbens was also reduced (Miczek et al., 2011). Although this study did not assess individual differences, it suggests that social defeat-induced adaptations within the VTA-nucleus accumbens circuitry that leads to depressive-like behaviors in rats may be opposite to that observed in mice. Another difference between these studies that could account for their opposing results is the extended duration of stress that rats were exposed to (5 weeks) as compared with mice (10 days). Despite the drastic differences on the effects of social stress on the VTA and BDNF system in rats and mice, the findings in rats are consistent with the overwhelming evidence that depression is related to a decrease in BDNF levels within other brain regions (Duman and Monteggia, 2006).

Interestingly, these dopamine neurons in the VTA are in part regulated by CRF. In particular, social defeat in rats produces a sensitized locomotor response to cocaine challenge and increased self-administration of cocaine and these effects are blocked by administration of CRF receptor antagonists into the VTA (Boyson et al., 2014). These results suggest that multiple factors acting within the VTA modulate dopamine function in socially defeated animals.

Other studies also point to the importance of the nucleus accumbens in regulating resilience/susceptibility. Increased expression of deltaFosB in the nucleus accumbens is associated with resilience to the social avoidant effects of chronic social defeat in mice compared to mice that were vulnerable to social anxiety (Vialou et al., 2010). Further deltaFosB is reduced in mice that are socially isolated and this is reversed by overexpressing deltaFosB in the nucleus accumbens (Donahue et al., 2014). These findings are translationally relevant since lower deltaFosB concentrations are observed in post mortem nucleus accumbens samples from depressed individuals. Further investigation suggested the importance of AMPA receptors, target genes of deltaFosB, with decreased AMPA receptor function (lower GluR1:GluR2 ratio) contributes to resilience. In vulnerable mice, BDNF protein is increased in the nucleus accumbens and knockdown of this BDNF did not alter the phenotype of stressed mice, but knockdown of BDNF in the VTA decreased the percentage of stressed mice that were susceptible to social anxiety (Krishnan et al., 2007). However, this is in contrast to data in rats (Altar et al., 1992) in which BDNF was low in both susceptible and resilient rats though these were characterized by their intracranial self-stimulation thresholds. Thus, the potential role of BDNF in mediating resilience may be stress-specific. In sum, the results suggest that increased activity of dopamine cells and of BDNF expression in these cells in the VTA is associated with susceptibility to social defeat. Importantly, projections of the VTA to the nucleus accumbens rather than the medial prefrontal cortex are involved and increased activity of accumbal cells throughout chronic stress exposure, as indicated by deltaFosB, is associated with resilience.

c. *Neuropeptide Y*

Neuropeptide Y (NPY) is yet another neuroendocrine peptide that has demonstrated central control over stress susceptibility. NPY is widely distributed in the brain and expressed in regions known for their involvement in psychiatric disorders. NPY is often co-expressed with the neuropeptide CRF and as such, it is poised to impact central regulation of neuroendocrine responses and stress-related behavior. For example, central administration of exogenous NPY has demonstrated anxiolytic properties in rodents and is capable of inhibiting the anxiogenic effects of CRF (Primeaux et al., 2005; Ehlers et al., 1997; Britton et al., 1997). In addition, stress-sensitive brain regions such as the locus coeruleus (LC) (Makino et al., 2000), the amygdala (Adrian et al., 1983), and the paraventricular nucleus (Baker and Herkenham, 1995) all highly express both neuropeptides and NPY is reported to oppose the effects of CRF in these regions (Britton et al., 2000; Heilig et al., 1994). One example occurs in the LC, where CRF serves as an excitatory neurotransmitter (Valentino et al., 1983) and NPY decreases the LC-noradrenergic neuronal firing (Illes et al., 1993). Consequently, central administration of NPY decreases NE overflow by acting on Y_1 receptors (Hastings et al., 2004). Because evidence of elevated LC activity has been linked to depression and PTSD (Wong et al., 2000; Geracioti et al., 2001) this NPY-induced brake on LC over activation may therefore promote stress resilience. In rodents, the WKY rat is proposed as an animal model of depression due to their inherent depressive-like behavior (Lopez-Rubalcava and Lucki, 2000). Tonic LC firing is increased in WKY rats as compared to non-depressive-like Wistar and Sprague Dawley rats (Bruzos-Cidon et al., 2014) and although NPY levels in the LC have not been assessed, plasma levels of NPY are three time lower in WKY rats as compared to Sprague Dawley rats (Myers et al., 1993). Furthermore, it has been established that NPY and NPY receptor mRNA is downregulated in the hippocampus and hypothalamus of rats and tree shrews following social defeat stress, although this study did not address differences in coping responses (Zambello et al., 2010). Since NPY has been established as an “anti-stress” neuropeptide studies have begun evaluating individual differences in NPY levels within susceptible and resilient populations of rats from the same strain. Decreased NPY levels were reported in the amygdala, hippocampus and periaqueductal gray of rats that were vulnerable to a predator-scent stress paradigm compared with the resilient phenotype (Cohen et al., 2012). In addition, NPY mRNA in the amygdala was negatively correlated with anxious behavior in rats characterized as exhibiting high or low levels of anxiety (Primeaux et al., 2006).

Notably, preclinical data linking NPY to resilience are relevant to findings in humans; deficiencies within the central NPY system have been demonstrated in patients with major depression (Widerlov et al., 1988). Individuals with combat-related PTSD also have significantly lower levels of NPY in their cerebrospinal fluid

(Rasmusson et al., 2000; Sah et al., 2014) and NPY levels recover during remission (Yehuda et al., 2006). Similarly, elevated levels of NPY were reported in highly resilient special operations soldiers (Morgan et al., 2000). The single prolonged stress model in rodents produces many behavioral and biochemical features of PTSD (Liberzon et al., 1997) and in a recent study, intranasal NPY effectively blocked or reversed many of the stress-related consequences (Serova et al., 2014, 2013). Several lines of evidence from studies in animals and humans point towards NPY in the psychobiology of resilience to stress-induced psychiatric disorders, while deficits of NPY in the brain are related to psychiatric disorders. Studies designed to evaluate NPY levels in rodents demonstrating differing coping strategies will be an important advancement in elucidating the neural basis of stress resiliency.

d. *Others*

A recent study suggests a role for Acetylcholinergic mechanisms in mediating resilience (Mineur et al., 2013). Cholinergic knockdown in the hippocampus produced social anxiety in a subthreshold model of social defeat in which behavioral changes are not observed. These effects could be reversed by fluoxetine treatment in the stressed animals. Other peptides, such as orexins and enkephalins, are the subject of considerable research and may be ultimately identified as additional substrates of resilience/vulnerability. Enkephalins acting via the mu-opioid receptor may also be important in mediating resilience. Mu-opioid receptor density in the locus coeruleus is increased in resilient rats in a model of social defeat potentially suggesting an increased inhibitory drive to locus coeruleus activity in resilient rats. This could reduce the stress-related effects of CRF but also be associated with a potential for opiate abuse (Chaijale et al., 2013).

9. Relationship of stress-related psychiatric disorders to other diseases/co-morbidities

In addition to the debilitating consequences of stress-related psychiatric disorders on mental health, suffering from depressive and anxiety disorders also increase the risk of developing comorbid medical disorders such as cardiovascular disease (Anda et al., 1993; Rugulies, 2002). Just as the coping response is known to impact one's susceptibility to psychiatric disorders, submissive personality traits or passively coping during chronic stress is linked to the pathogenesis of hypertension (Harburg et al., 1964; Julius et al., 1981; Esler et al., 1977) while active coping is related to resiliency (Southwick et al., 2005).

Animal models of social stress have found passive coping to have a similar impact on cardiovascular health; rats exposed to social stress exhibit exaggerated reductions in resting heart rate variability 24–48 h after the 7th and final exposure to social stress, indicating a shift towards sympathetic control of heart rate and was exaggerated in rats displaying passive coping responses (Wood et al., 2012). In a related study, intruders adopting a proactive response to social stress by countering the resident's attacks displayed smaller and shorter lasting disturbances of circadian rhythm of heart rate following social stress compared to rats that adopted a more passive response (Meerlo et al., 1999). Furthermore, a study in which rats were classified as passive or active copers prior to chronic intermittent stress reported the association between passive coping and hypertension (Hawley et al., 2010). Adaptations within the brain that are related to passive and active coping and central to depression and cardiovascular disease will be critical to better understanding the etiology of depression-cardiovascular disease comorbidity.

In addition to precipitating psychiatric disorders, there is also a strong clinical association between social stress and urological disorders. Traumatic social stressors such as a broken marriage or loss of a loved one have been reported to produce urinary retention (Fenster and Patterson, 1995). Childhood physical or sexual abuse is also associated with urinary retention disorders in adulthood (Davila et al., 2003) (Romans et al., 2002). Consequently, psychiatric disorders are related to an increased incidence and greater severity of urological disorders (Johnson et al., 2010). Animal models of social stress have shed some light on the etiology of stress-related urological disorders. For example, rats exposed to social defeat stress exhibit urinary retention (Wood et al., 2009; Desjardins et al., 1973). Recent studies confirmed that this stress-related urinary dysfunction is mediated by increases in CRF within Barrington's nucleus, a brain region involved in micturition (Wood et al., 2013b); both a CRF1 antagonist and shRNA targeted knockdown of CRF in Barrington's nucleus inhibited the development of urinary dysfunction evident in socially defeat rats. These studies did identify that bladder hypertrophy was negatively correlated with the latency to assume a submissive posture, demonstrating an association between passive coping and bladder dysfunction (Wood et al., 2009). However, preclinical studies identifying mechanisms of individual differences in susceptibility to stress-related urological dysfunction are lacking.

10. Conclusions

Overall, it seems clear that there are multiple neural determinants of resilience or vulnerability to stress. Peptides such as CRF and NPY and the VTA/dopamine system have been the best-characterized mediators of resilience or vulnerability. The bulk of evidence suggests that resilience is not simply the opposite of vulnerability because there are some mechanisms that are dichotomous in resilient vs. vulnerable animals. How these diverse mechanisms interact with one another to produce a resilient or vulnerable phenotype is challenging. Further adding to this complexity is the idea that resilience is also a dynamic process (Bracha et al., 2004; Rutter, 2006). The phenotypes associated with resilience may be stressor specific so that an individual resilient in one stress context to certain outcomes may not be resilient in a different context and/or to other outcomes. Maintaining the same resilient phenotype when the stressful environment shifts may not necessarily be adaptive so resilience phenotypes may have to be adjusted to suit changing environments.

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