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Dominance status alters restraint-induced neural activity in brain regions controlling stress vulnerability

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ABSTRACT

Understanding the cellular mechanisms that control resistance and vulnerability to stress is an important step toward identifying novel targets for the prevention and treatment of stress-related mental illness. In Syrian hamsters, dominant and subordinate animals exhibit different behavioral and physiological responses to social defeat stress, with dominants showing stress resistance and subordinates showing stress vulnerability. We previously found that dominant and subordinate hamsters show different levels of defeat-induced neural activity in brain regions that modulate coping with stress, although the extent to which status-dependent differences in stress vulnerability generalize to non-social stressors is unknown. In this study, dominant, subordinate, and control male Syrian hamsters were exposed to acute physical restraint for 30 min and restraint-induced c-Fos immunoreactivity was quantified in select brain regions. Subordinate animals showed less restraint-induced c-Fos immunoreactivity in the infralimbic (IL), prelimbic (PL), and ventral medial amygdala (vMeA) compared to dominants, which is consistent with the status-dependent effects of social defeat stress. Subordinate animals did not show increased c-Fos immunoreactivity in the rostroventral dorsal raphe nucleus (rvDRN), which is in contrast to the effects of social defeat stress. These findings indicate that status-dependent changes in neural activity generalize from one stressor to another in a brain region-dependent manner. These findings further suggest that while some neural circuits may support a generalized form of stress resistance, others may provide resistance to specific stressors.

1. Introduction

A great deal of individual variation exists in vulnerability to the negative consequences of stressful life events. Although stress is a risk factor for a wide range of health problems, only a small portion of individuals exposed to stressful events develop stress-related psychopathology [1,2]. Stress resilience refers to an individual's capacity to cope with adversity and avoid the negative behavioral and physiological consequences that would otherwise impair physical and psychological well-being [3]. In the past decade, several animal models have been used to investigate the cellular and molecular mechanisms of stress resilience. This body of work indicates that stress resilience is characterized by active processes involving specific cellular and molecular mechanisms, rather than simply a lack of deleterious behavioral and physiological responses [4]. An improved understanding of the neurobiological mechanisms underlying stress resilience can lead to plausible targets for the treatment of a wide range of stress-related mental illnesses.

Several environmental factors that produce experience-dependent neuroplasticity and reduce the effects of subsequent stressful events have previously been identified. The opportunity to exert behavioral control over a stressor by terminating its occurrence blunts the behavioral and neurochemical consequences of an aversive event and prevents the heighten anxiety and impaired escape behavior characteristic of learned helplessness [5]. Rats exposed to uncontrollable tail shocks show elevated neural activity of serotonin (5-HT) neurons in the dorsal raphe nucleus (DRN), which is essential for the development of learned helplessness [6]. Interestingly, animals that experience controllable tail shocks exhibit neural plasticity in the prelimbic cortex (PL) that inhibits DRN activity and prevents the development of learned helplessness when they are later faced with uncontrollable stress [7,8]. Furthermore, prior experience with controllable shock prevents elevated 5-HT concentrations in the DRN after social defeat and prevents the impaired escape latencies and social interaction deficits associated with social defeat stress [9]. Together, these findings suggest that experience with a controllable stressor produces a generalized stress resistance to both

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uncontrollable tail shock and social defeat stress.

Environmental enrichment is another factor that modulates behavioral and physiological responses to stress and thereby promotes stress resistance. Exposure to an enriched housing environment prior to social defeat stress reduces defeat-induced social avoidance and increases FosB/ΔFosB immunoreactivity in the PL, infralimbic cortex (IL), anterior cingulate, and nucleus accumbens [10]. Interestingly, lesions of the IL disrupt the protective effects of environmental enrichment and decrease FosB/ΔFosB immunoreactivity in the PL, anterior cingulate, and nucleus accumbens. These findings suggest that the IL plays a key role in the cellular mechanisms by which environmental enrichment promotes stress resilience. However, not all forms of experience-dependent stress resistance depend on neural activity in the medial prefrontal cortex (vmPFC) or its PL and IL subregions. Voluntary exercise promotes resistance to the exaggerated fear conditioning and impaired escape learning characteristic of learned helplessness, although exercise-dependent resistance is not lost following lesions of the vmPFC [11]. All together, these findings suggest that multiple brain regions and neurochemical signals contribute to stress resilience.

Different types of resiliency training appear to generate varied forms of experience-dependent neuroplasticity and, perhaps, resistance to distinct stressors. We have used dominance relationships in Syrian hamsters to investigate the mechanisms by which social status reduces the behavioral and physiological effects of subsequent social defeat stress. In Syrian hamsters, acute social defeat leads to a conditioned defeat response, which is characterized by a decrease in normal territorial aggression and an increase in submissive and defensive behavior in future social interactions [12]. A great deal of information indicates that the conditioned defeat response is an ethologically relevant form of conditioned fear. Several cellular and molecular mechanisms that regulate synaptic plasticity within the basolateral amygdala (BLA) are critical for the acquisition of conditioned defeat, including the activity of NMDA receptors, cyclic AMP response element binding protein, brain-derived neurotropic factor, and activity-regulated cytoskeletal-associated protein [13–16]. In addition, neurotransmission in several cortical, limbic, and hindbrain regions modulate both the acquisition and expression of conditioned defeat, including the BLA, central amygdala (CeA), medial amygdala (MeA), bed nucleus of the stria terminalis (BNST), lateral septum (LS), nucleus accumbens (NAcc), ventral hippocampus (vHP), vmPFC, and DRN [17–23]. Dominant hamsters exhibit a reduced conditioned defeat response, whereas subordinates exhibit an elevated conditioned defeat response compared to controls that do not have experience maintaining a dominance relationship [24]. The maintenance of dominant social status also leads to elevated defeat-induced c-Fos immunoreactivity in the PL, IL, and ventral MeA (vMeA) [25]. On the other hand, vulnerability to the effects of social defeat stress in subordinate hamsters is associated with elevated c-Fos immunoreactivity in select subdivisions of the DRN [26]. These findings suggest that neural activity in certain limbic brain regions supports stress resistance in dominant hamsters, while neural activity in hindbrain regions such as the DRN promotes stress susceptibility in subordinates.

Despite growing literature on the cellular and molecular mechanisms of stress resilience, there has been relatively little effort focused on better understanding the common neural correlates of coping with different types of stressors. The present study is focused on whether the cellular mechanisms controlling status-dependent differences in responses to social defeat stress generalize to acute physical restraint. Previous research indicates these stressors share some commonalities. Social defeat and physical restraint increase c-Fos expression within the lateral hypothalamus and the dorsal premammillary nucleus, which is thought to reflect activation of septo-hippocampal circuits that encode entrapment and restriction of environmental boundaries [27]. The goal of the present study is to determine whether the pattern of neural activation associated with vulnerability and resistance to social defeat stress in subordinate and dominant hamsters generalizes to restraint stress.

2. Methods

2.1. Animals

Male Syrian hamsters (*Mesocricetus auratus*) were obtained from our breeding colony derived from animals purchased from Charles River Laboratories (Wilmington, MA, USA). Animals were 3–4 months of age and weighed 120–180 g at the start of the study. All animals were individually housed in polycarbonate cages (12 cm × 27 cm × 16 cm) with corncob bedding, cotton nesting materials, and wire mesh tops. Food and water were available ad libitum. Animals were housed in a temperature-controlled colony room (21 ± 2 °C) and kept on a 14:10-h light/dark cycle. All behavioral testing occurred during the first 3 h of the animals' active period. Cages were not changed for at least one week prior to testing to allow individuals to scent mark their territory. Subjects were individually housed and handled before dominant–subordinate encounters in order to habituate them to the stress of human handling. All procedures were approved by the University of Tennessee Institutional Animal Care and Use Committee (IACUC) and are in concordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Dominance encounters

Twenty-six animals were weight-matched and assigned to resident–intruder dyads. Resident or intruder status was randomly assigned and animals were exposed to daily dyadic encounters for two weeks. All encounters occurred in the resident's home cage and dominance status was found to be unrelated to residency status. Hamsters initially greet and sniff each other before one animal initiates aggression and the other responds with submissive and defensive behavior. Dominant animals are identified by their consistent display of aggressive behavior (e.g. chasing, attacking, biting, and displaying upright and side offensive postures), and subordinates are identified by their consistent display of submissive and defensive behavior (e.g. fleeing, avoiding partner, displaying upright and side defensive posture, tail-up, and stretch-attend postures). While mild aggressive postures are often observed during the first encounter, attacks from the dominant animal and a clear asymmetric pattern of agonistic behavior may not emerge for up to five days. We use 10-min encounters to encourage social investigation prior to the formation of a dominance relationship. After a dominance relationship is formed, we use 5-min encounters to maintain the relationship and prevent wounding of the subordinate. Using this model, we have found that dominance relationships remain stable for at least two weeks [24,28]. Dyads that failed to establish a clear and stable dominance relationship by the fifth encounter were excluded from analysis (n = 4 dyads). To control for social status, a separate cohort of animals was individually housed and not exposed to daily dyadic encounters.

2.3. Restraint stress

Twenty-four hours after the final dominance encounter, hamsters were placed in ventilated Plexiglas restraint tubes to confine their movement. Dominants (n = 13), subordinates (n = 13), and social status controls (n = 11) were exposed to restraint stress for 30 min. An additional cohort of animals (n = 11) was not exposed to restraint stress or daily dominance encounters, and these animals were considered handled controls.

Because Syrian hamsters are burrowing animals with a high degree of flexibility, the effectiveness of a physical restraint stressor should be verified. Although some investigators have shown that acute physical restraint increases plasma cortisol in Syrian hamsters [29], others report that hamsters fall asleep in restraint tubes and use high intensity