Hypothalamic Oxytocin Mediates Social Buffering of the Stress Response

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Background: While stressful life events can enhance the risk of mental disorders, positive social interactions can propagate good mental health and normal behavioral routines. Still, the neural systems that promote these benefits are undetermined. Oxytocin is a hormone involved in social behavior and stress; thus, we focus on the impact that social buffering has on the stress response and the governing effects of oxytocin.

Methods: Female prairie voles (*Microtus ochrogaster*) were exposed to 1 hour immobilization stress and then recovered alone or with their male partner to characterize the effect of social contact on the behavioral, physiological, and neuroendocrine stress response. In addition, we treated immobilized female voles recovering alone with oxytocin or vehicle and female voles recovering with their male partner with a selective oxytocin receptor antagonist or vehicle. Group sizes varied from 6 to 8 voles ($N = 98$ total).

Results: We found that 1 hour immobilization increased anxiety-like behaviors and circulating levels of corticosterone, a stress hormone, in female prairie voles recovering alone but not the female prairie voles recovering with their male partner. This social buffering by the male partner on biobehavioral responses to stress was accompanied by increased oxytocin release in the paraventricular nucleus of the hypothalamus. Intra-paraventricular nucleus oxytocin injections reduced behavioral and corticosterone responses to immobilization, whereas injections of an oxytocin receptor antagonist blocked the effects of the social buffering.

Conclusions: Together, our data demonstrate that paraventricular nucleus oxytocin mediates the social buffering effects on the stress response and thus may be a target for treatment of stress-related disorders.

Key Words: Corticosterone, elevated plus maze, HPA axis, immobilization stress, pair-bond, social buffering

Stressful life events (e.g., divorce or death of a spouse) are deleterious to adult mental health in humans (1,2), and the social environment can either propagate or attenuate these effects. For example, depression is concomitant with the lack of social support following a stressful life event (2). In contrast, close relationships ameliorate stress-induced biobehavioral responses and reduce the risk of psychological disorders in humans (3,4). For instance, the natural occurrence of physical touch with an infant during prefeeding behaviors and nursing is sufficient to reduce the anxiety experienced by mothers during physical and psychological stress (5). This social buffering effect has also been observed through contact with a committed partner, reducing the negative impact of stress (e.g., suffering from a panic disorder or psychological distress) (3,4). Still, the neuroendocrine mechanisms underlying social buffering via committed partnerships are not well understood. Further, there is limited modeling of this phenomenon in animal research, as less than 3% of mammalian species display social bonding between partners.

The prairie vole (*Microtus ochrogaster*) is a socially monogamous rodent that forms long-term pair bonds between partners (6). These bonds may protect against the aversive effects of stress by attenuating the action of the hypothalamic-pituitary-adrenal (HPA) axis (7). For example, while prolonged social separation elevates basal levels of corticosterone and increases a depression-like response to acute psychological stressors (8), social pairing can reduce basal corticosterone levels (9,10). Further, reunion with a social partner can attenuate the HPA axis response associated with separation (11). Several neuroendocrine systems, including oxytocin (OT), vasopressin (AVP), and corticotrophin-releasing hormone (CRH), are involved in prairie vole pair bonds (4,6). Interestingly, these systems are vital to the regulation of the stress-induced HPA axis activation. In response to stress, the paraventricular nucleus (PVN) of the hypothalamus releases CRH and AVP to promote a signaling cascade, leading to an increase in circulating corticosterone and an induction in psychological and behavioral pathologies (4). In contrast, OT released from the PVN in rats acts as an anxiolytic—suppressing HPA axis function (12). Therefore, the neuroendocrine systems that are impetuses to adult social bonds may also regulate the social buffering of the stress response.

We investigated the biobehavioral effects and underlying neuroendocrine mechanisms of social buffering in female prairie voles. We established a behavioral paradigm demonstrating recovery with a male partner following immobilization stress decreases the biobehavioral stress response while promoting activity of the OT system in the PVN. We then focused on the functional role of the OT system in social buffering and demonstrated that social recovery following stress facilitates OT release in the PVN to promote social buffering.

Methods and Materials

Detailed methods and experimental design are provided in Supplement 1.

Results

Social Support Attenuated Behavioral and Hormonal Responses to Immobilization Stress

We characterized the impact of recovering with a male partner following immobilization on the behavioral and hormonal

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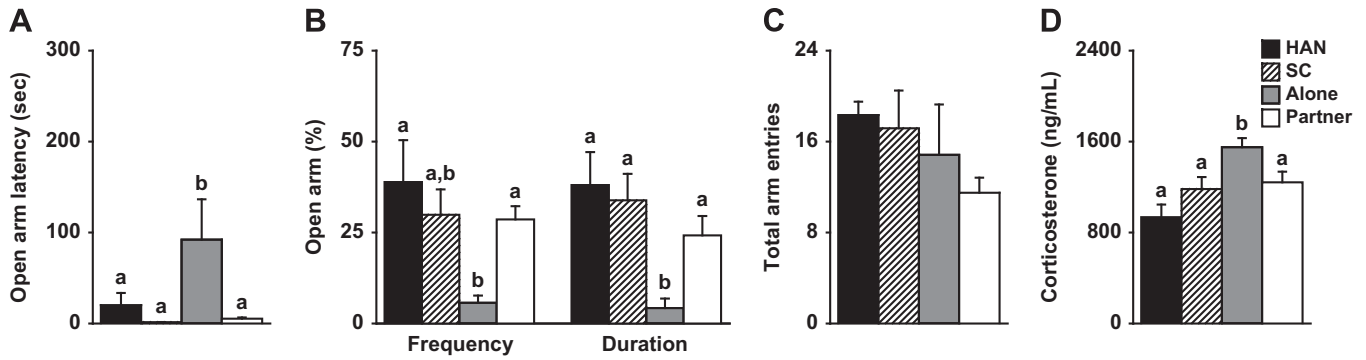

Figure 1. Social support attenuated the behavioral and hormonal stress response 30 minutes postimmobilization. **(A, B)** Immobilized female voles recovering alone (Alone) displayed a substantial increase in elevated plus maze (EPM) anxiety-like behaviors, including delayed open arm latency, fewer open arm entries, and reduced open arm duration. By contrast, female voles recovering with their social partner (Partner) displayed low anxiety-like behavior similar to the handle control animals (HAN). **(C)** These effects seemed to be behavior-specific, as total arm entries, a locomotor measure, did not vary between groups. **(D)** In addition to elevated EPM anxiety-like behavior, immobilized female voles recovering alone displayed a rise in circulating corticosterone concentrations, but female voles recovering with their male social partner had corticosterone levels similar to HAN control animals. Social control animals (SC) are nonimmobilized female voles removed from their social partner for 30 minutes before the EPM test. Bars labeled with different letters differ significantly by post hoc Student-Newman-Keuls test in which a significant main effect was detected in the analysis of variance ($p < .05$). Data are expressed as mean ± SEM.

response in female prairie voles. Pair-bonded female voles received 1-hour immobilization, recovered either alone or with their male partner for 30 minutes, and were examined for anxiety-like behaviors in an elevated plus maze (EPM) test and circulating levels of corticosterone. Immobilized female voles recovering alone displayed a substantial increase in EPM anxiety-like behaviors, including delayed open arm latency ($F_{3,17} = 4.93$, $p < .05$), fewer open arms entries ($F_{3,22} = 3.86$, $p < .05$), and reduced open arm duration ($F_{3,22} = 5.14$, $p < .01$) compared with the handled control animals (Figure 1A,B), similar to our previous reports (13). The former also had a rise in circulating corticosterone compared with the latter ($F_{3,21} = 6.32$, $p < .01$; Figure 1D). By contrast, recovering with a male partner following immobilization attenuated anxiety-like behaviors and blunted the rise in circulating corticosterone, mirroring responses in the handled control animals. This effect was behavior-specific, as locomotor behavior was similar for all groups (Figure 1C). Furthermore, as prairie voles are sensitive to social separation, which may affect HPA axis function and EPM performance (8,14,15), we included a cohort of nonimmobilized female prairie voles that were removed from their male partner during the 30-minute recovery period (i.e., social control). These female voles did not differ from the handled control animals in anxiety-like behaviors or circulating levels of corticosterone (Figure 1). Together, these data demonstrate that the immobilization-induced stress response can be buffered by a bonded partner.

Social Support Suppressed Female Stress-Related Behaviors and Promoted Dyadic Interaction

We further evaluated the behavioral stress response by comparing the occurrence of stress-related behaviors (i.e., rearing, repetitive autogrooming, and route tracing) for 1 hour while female prairie voles remained undisturbed in their home enclosures with their male partner and again for 1 hour postimmobilization while they recovered alone or with their male partner. We observed immobilization-induced changes in stress-related behaviors in the recovery chamber compared with baseline conditions that were dependent on the social environment (stress index frequency, $t_{11} = 4.00$, $p < .005$; stress index duration, $t_{11} = 3.83$, $p < .005$; Figure 2A,B). Specifically, female prairie voles that recovered alone displayed a significant increase in these stress-related behaviors, namely route tracing (frequency, $t_5 = 3.07$, $p < .05$; duration, $t_5 = 2.70$, $p < .05$) and repetitive autogrooming (frequency, $t_5 = 4.37$, $p < .01$; duration, $t_5 = 4.82$, $p < .005$). These effects were noted during the first 30 minutes following immobilization, returning to baseline levels 30 minutes later (Table S1 in Supplement 1). We observed no changes in stress-related behaviors initially among immobilized female prairie voles recovering with their male partner (Figure 2A,B). After interacting with their male partner for 30 minutes, autogrooming behavior was suppressed (frequency, $t_6 = -2.73$, $p < .05$; duration, $t_6 = -3.06$, $p < .05$; Table S1 in Supplement 1). Route-tracing behavior was not different at this latter period compared with baseline (Table S1 in Supplement 1). However, this null effect may be due to the fact that seven of the eight female prairie voles recovering with their male partner never displayed this behavior during the baseline condition (inducing a flooring effect). These data suggest that the occurrence of stress-related behaviors was augmented by immobilization and suppressed via social recovery.

In humans and other gregarious mammals, stress can stimulate social-seeking behaviors (16). Further, group members can reduce anxiety by increased prosocial behaviors—behavior that is performed for the benefit of others—directed toward distressed individuals (4). In the current study, we did not observe a substantive change in female social behaviors after immobilization (Figure 2C,D; Table S1 in Supplement 1). However, male prairie voles augmented their social behaviors during the first 30 minutes when their female partner returned from immobilization —approaching (frequency, $t_6 = 2.91$, $p < .05$), sniffing (frequency, $t_6 = 2.74$, $p < .05$), and grooming (frequency, $t_6 = 3.80$, $p < .01$; duration, $t_6 = 3.31$, $p < .05$) the female more often (Figure 2E,F). Such effects were not observed in the subsequent 30 minutes (Table S1 in Supplement 1). Only one of the eight pairs was observed mating during the prestress and poststress periods. Therefore, as female prairie voles recovered from immobilization with their male partner, they experienced an enhanced social display from their male partner and concomitantly displayed less stress-related behaviors.

Immobilization Affected Neuropeptide Receptor Content in a Brain Region-Specific Manner

Western blotting revealed the 1-hour immobilization reduced the content of OT receptors (OTR) ($F_{3,19} = 5.37$, $p < .01$;