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Research report

Levels of central oxytocin and glucocorticoid receptor and serum adrenocorticotropic hormone and corticosterone in mandarin voles with different levels of sociability

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HIGHLIGHTS

- Low social voles display higher levels of anxiety.
- Low social voles display more serum ACTH and CORT.
- High social voles display more GR-ir neurons in the hippocampus.
- High social voles display more OT-ir neurons in the PVN and SON.

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ABSTRACT

Sociability is the prerequisite to social living. Oxytocin and the hypothalamo-pituitary-adrenocortical axis mediate various social behaviors across different social contexts in different rodents. We hypothesized that they also mediate levels of non-reproductive social behavior. Here we explored naturally occurring variation in sociability through a social preference test and compared central oxytocin, glucocorticoid receptors, serum adrenocorticotropic hormone and corticosterone in mandarin voles with different levels of sociability. We found that low-social voles showed higher levels of anxiety-like behavior in open field tests, and had more serum adrenocorticotropic hormone and corticosterone than high-social voles. High-social individuals had more glucocorticoid receptor positive neurons in the hippocampus and more oxytocin positive neurons in the paraventricular nuclei and supraoptic nuclei of the hypothalamus than low-social individuals. Within the same level of sociability, females had more oxytocin positive neurons in the paraventricular nuclei and supraoptic nuclei of the hypothalamus than males. These results indicate that naturally occurring social preferences are associated with higher levels of central oxytocin and hippocampus glucocorticoid receptor and lower levels of anxiety and serum adrenocorticotropic hormone and corticosterone.

1. Introduction

Living in social groups is clearly beneficial for many species, and can result in increased survival, enhanced group fitness and the progression of brain development and cognitive abilities [1,2]. Vertebrate species display social interactions of vast quality and quantity, and a wide array of social behaviors [2]. Monogamous species usually exhibit high levels of social behavior among individuals, biparental care of offspring, selective aggression toward unfamiliar conspecifics and social preferences. In contrast, non-monogamous species tend to be solitary, less affiliative and more aggressive [3]. Thus, monogamous species are considered more social than polygamous species. The most basic definition of prosocial behavior includes any behavior that brings two or more individuals into close proximity [1]. However, most studies into prosocial behavior focus on affiliative behavior between mothers and offspring, and between mates in different social contexts in rodents [4,5], and little attention has been given to prosocial behavior in a non-reproductive context and naturally occurring variation in sociability.

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Central oxytocin (OT) is implicated in a variety of prosocial behaviors in a reproductive context, such as pair-bonding, maternal or sexual behaviors [6–10]. OT also mediates prosocial behavior in a non-reproductive context in various rodents and in humans. For example, in rats, chronic central OT administration increases social interactions between males and females [11]. In meadow voles (*Microtus pennsylvanicus*), OT facilitates same-sex social preferences between females [12] and in people, intranasal or intravenous OT promotes social approach and comprehension in autistic patients [13–16]. In social species, the ability to recognize others is a fundamental prerequisite to many social behaviors [17] and OT mediates social recognition [17,18]. In rats, ICV injections of OT facilitate social recognition and can be blocked by an OT antagonist [19–21]. OT KO mice have impaired social recognition and this social recognition deficit can be rescued through OT infusion [22]; and OT receptor (OTR) KO mice also show impaired social recognition [23]. Since OT plays a large role in prosocial behavior and social recognition, we predict that naturally occurring variation in sociability may be associated with levels of central OT.

The hypothalamo-pituitary-adrenocortical (HPA) axis is a key regulator of systemic homeostasis and its stimulation culminates in the secretion of glucocorticoid hormones that act on multiple peripheral effectors as well as the brain to promote adaptation to adversity [24]. Repeated or increased HPA axis activation is often related with chronic or severe stress and produces negative physiological effects and induces profound changes in behavior, such as social avoidance and anxiety [25–27]. However, the effects of the HPA axis on social preference are dose dependent. In male prairie voles, a low dose of corticotropin-releasing factor (CRF) facilitates the formation of social preferences, but at doses 10–100 times higher than those effective in producing partner preferences, CRF has deleterious effects on social bonding [28]. HPA axis activity mediates emotional reactions accompanied by elevated serum adrenocorticotropic hormone (ACTH) and corticosterone (CORT), and negative emotions leading to negative behaviors (aggressive behavior and social avoidance) associated with low sociability [29,30]. Higher levels of hippocampus glucocorticoid receptor (GR) enhance negative-feedback of the HPA response, and subsequently reduce levels of depression and anxiety-like behavior [31]. A large body of research has emphasized a role for the HPA axis in the enhancement of memory consolidation [17]. CORT has recently been shown to facilitate social learning in the social transmission of food preferences [32]. Since the HPA axis play a large role in emotional responses, social behavior and social recognition, we predict that variability in sociality may also be associated with levels of ACTH, CORT, anxiety and hippocampus GR.

The mandarin vole (*Microtus mandarinus*) is a highly social rodent widely distributed across China [33]. Males and females form selective partner preferences, display high levels of social behavior and paternal care and exhibit socially monogamous characteristics [33,34]. Neonatal paternal deprivation impairs social recognition and sociability and alters levels of OT and serum stress hormone in mandarin voles [35,36]. Mandarin voles from different populations display different levels of sociability [37], as do dominant and subordinate voles (accompanied by different distributions of OT and AVP in the brain) [38]. Mandarin voles are ideal animals for investigating relationships between sociability, HPA axis activation and central OT. If the hypothesis that OT and the HPA axis mediate high and low sociability is true, there should be different distributions of central OT, hippocampus GR and serum stress hormone. Here we compared levels of central OT and hippocampus GR in male and female mandarin voles with different levels of sociability. Our aim was to determine whether the degree of sociability is related to emotional responses in open field tests and whether the HPA axis is linked to variation in sociability.

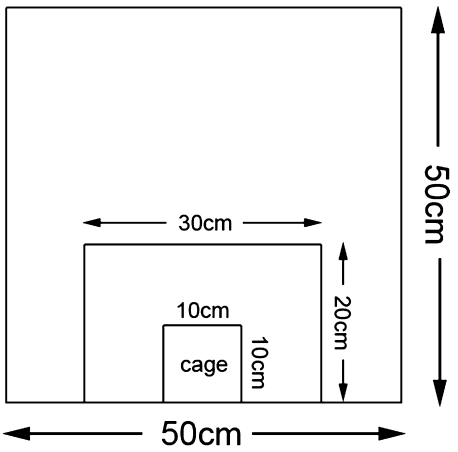

Fig. 1. Graph of cage used for social preference tests.

2. Methods

2.1. Subjects

Subjects were laboratory-reared mandarin voles originating from a wild population in Henan, China. Voles were weaned at 21 days of age and housed in same-sex sibling pairs prior to and after the behavioral test in plastic cages (length × width × height: 44 cm × 22 cm × 16 cm) containing wood shavings as bedding. Water, carrots and standard rabbit chow (Xian Jiaotong University Laboratory Animal Center, Xian, China) were freely available. The colony room was maintained on a 14:10 h light/dark cycle (lights on at 20:00 h) and at 23 ± 2 °C. Mandarin voles are nocturnal and all behavioral tests were conducted during their active phase.

2.2. Social preference tests

The social preference paradigm in mandarin voles (male, $n = 63$; female, $n = 63$; 45 days of age) was based on an established behavioral test [39,40]. In females, estrogen secretion changes dramatically along with oestrus cycle, and females in diestrous have relatively stable estrogen secretion. Therefore, females were all diestrous, and the oestrous stage of adult females was checked and determined by cell types in vaginal smears [41]. Tests were conducted between 8:00 and 11:00 h. Prior to testing voles were placed in a novel arena. The arena was made of white glacial polyvinyl chloride (length × width × height: 50 cm × 50 cm × 25 cm). After 5 min of habituation, an empty wire-mesh cage (object stimulus; length × width: 10 cm × 10 cm) was placed near one side wall of the arena for 10 min (Fig. 1). The empty cage was then exchanged for another identical cage containing an unknown same-sex conspecific (social stimulus) for an additional 10 min. After each test we cleaned the cage with 30% alcohol solution and let the cage dry completely in another room.

Each test procedure was videotaped and scored and quantified afterwards using OBSERVER (V5.0; Noldus, NL). The duration of investigation of the object and social stimulus were scored as the time voles spent near the cage (length × width: 30 cm × 20 cm) with or without stimulus voles (the duration of direct investigation of the object and social stimulus were also scored). The duration of investigation of social stimulus minus the duration of time spent investigating the object was regarded as the pure investigation time of the social stimulus. Individual sociability was defined using established methods [42]. High sociability was defined as a pure duration of investigation of the social stimulus greater than 1 standard deviation (SD) above the mean. Low sociability was