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Early life stress impairs social recognition due to a blunted response of vasopressin release within the septum of adult male rats

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Summary Early life stress poses a risk for the development of psychopathologies characterized by disturbed emotional, social, and cognitive performance. We used maternal separation (MS, 3 h daily, postnatal days 1—14) to test whether early life stress impairs social recognition performance in juvenile (5-week-old) and adult (16-week-old) male Wistar rats. Social recognition was tested in the social discrimination test and defined by increased investigation by the experimental rat towards a novel rat compared with a previously encountered rat. Juvenile control and MS rats demonstrated successful social recognition at inter-exposure intervals of 30 and 60 min. However, unlike adult control rats, adult MS rats failed to discriminate between a previously encountered and a novel rat after 60 min. The social recognition impairment of adult MS rats was accompanied by a lack of a rise in arginine vasopressin (AVP) release within the lateral septum seen during social memory acquisition in adult control rats. This blunted response of septal AVP release was social stimulus-specific because forced swimming induced a rise in septal AVP release in both control and MS rats. Retrodialysis of AVP (1 μg/ml, 3.3 μl/min, 30 min) into the lateral septum during social memory acquisition restored social recognition in adult MS rats at the 60-min interval. These studies demonstrate that MS impairs social recognition performance in adult rats, which is likely caused by blunted septal AVP activation. Impaired social recognition may be linked to MS-induced changes in other social behaviors like aggression as shown previously.

1. Introduction

Child abuse or neglect are severe risk factors for the development of inappropriate and abnormal social and emotional behaviors including excessive aggression, increased anxiety, and depression (Widom, 1989; Barnow et al., 2001; Heim and

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Nemeroff, 2001; Heim et al., 2008; Weder et al., 2009). To provide insights into underlying brain mechanisms maternal deprivation paradigms have been developed to simulate human child maltreatment conditions in rodents (Ladd et al., 2000; Sanchez et al., 2001; Veenema, 2009). For example, separating pups from their mother daily on postnatal days 1–14 induces long-lasting changes in stress coping and emotional behaviors in rats (Plotsky and Meaney, 1993; Wigger and Neumann, 1999; Kalinichev et al., 2002) and mice (Romeo et al., 2003; Veenema et al., 2007). Recently, we showed that this maternal separation (MS) paradigm increases offensive-like behaviors during juvenile play-fighting (Veenema and Neumann, 2009) and increases aggression during adult resident-intruder encounters (Veenema et al., 2006; Veenema and Neumann, 2009) in male rats. These findings suggest that early life stress affects social communication.

Social communication relies on the ability to recognize and discriminate between individuals. In rodents, social recognition depends on detection of olfactory signals by the main and accessory olfactory systems perceived by anogenital investigation of the conspecific. Olfactory information is processed by limbic brain areas including the medial amygdala and the lateral septum (Richter et al., 2005; Baum and Kelliher, 2009; Sanchez-Andrade and Kendrick, 2009). Within the lateral septum, the neuropeptide arginine vasopressin (AVP) plays an essential role. For example, septal infusions of AVP improve social recognition in male rats, whereas infusions of AVP V1a receptor (V1aR) antagonists impair it (Dantzer et al., 1988; Engelmann and Landgraf, 1994; Everts and Koolhaas, 1997, 1999). Likewise, social recognition is impaired in V1aR knockout mice but rescued by restoring V1aR expression using viral vector-mediated gene transfer into the septum (Bielsky et al., 2005). Correspondingly, viral vector-mediated over-expression of septal V1aR prolongs social recognition in male rats and mice (Landgraf et al., 2003; Bielsky et al., 2005). These studies suggest that AVP via activation of septal V1aR plays a critical role in social recognition. However, information on the *endogenous* release of AVP within the lateral septum during the acquisition of social recognition memory is lacking.

We hypothesized that MS impairs social recognition and does so by influencing the release of AVP. We demonstrate that MS impairs social recognition memory in adult, but not juvenile, rats. We find that in contrast to non-separated (control) rats, adult MS rats do not show an increase in septal AVP release during the acquisition of social recognition memory. We also show that social recognition can be restored in adult MS rats by administering AVP locally in the lateral septum.

2. Methods

2.1. Animals

Wistar rats were obtained from Charles River (Sulzfeld, Germany) and maintained under standard laboratory conditions (12 h light/dark cycle, lights on at 0600 h, 22 °C, 60% humidity, food and water ad libitum). After one week of habituation, males and females were mated for five days. Females were subsequently housed in same-sex groups of four to six rats. During the last week of gestation, female rats were individually housed in standard rat cages (42 cm × 27 cm × 18 cm). The animal studies were conducted in accordance with the Guide for the Care and Use of Laboratory Animals of the Government of Oberpfalz and the guidelines of the NIH.

2.2. MS procedure

MS was performed as described earlier (Veenema et al., 2006). Briefly, on the day after parturition, i.e. on postnatal day 1, each litter was culled to eight to ten pups (in each nest two to four females). Litters were separated from the mother daily between 0900 h and noon from postnatal day 1 to 14. To do so, each dam was placed into a separate cage and the litter was transferred to an adjacent room and kept in a box filled with bedding and placed on a heating pad maintained at 30–33 °C. After 3 h, litters were returned to the home cage followed by the dam. Control litters were left undisturbed. Change of bedding occurred on postnatal day 1, 7 and 14 for both control and MS litters. Pups were weaned on postnatal day 21 and housed in sex- and treatment-matched groups of four to five rats until the start of the experiments. No more than two male pups per litter were used for each of the experiments.

2.3. Social discrimination test

The ability of juvenile (5-week-old) and adult (16-week-old) control and MS rats to discriminate between a previously encountered (*same*) and a *novel* 3-week-old male rat was tested according to Engelmann et al. (1995) with some minor modifications. Control and MS rats were individually housed in an experimental cage (40 cm × 24 cm × 35 cm) with bedding from their home cage for either 2 h (Exp. 1) or 2 days (Exp. 2 and 3). A 3-week-old rat was introduced into the cage of the experimental rat for 4 min (social memory acquisition period); either 30, 60 or 120 min later, the *same* 3-week-old rat was reintroduced along with a *novel* 3-week-old rat for 4 min (social discrimination period). Repeated testing took place at different days with new sets of 3-week-old rats. Tests were performed between 1300 h and 1600 h. All tests were videotaped and the time spent in investigating the 3-week-old rats (sniffing the anogenital and head/neck regions) was measured by a researcher blinded to the treatment condition using Eventlog (version 1.0, October 1986, R. Hedersen). The percentage of time investigating the *same* and the *novel* rat (time investigating *same* or *novel* rat/time investigating *same* + *novel* rat × 100%) was measured. A significantly lower investigation time directed towards the *same* versus the *novel* rat was interpreted as social recognition. Note that the 3-week-old rats did not elicit play behavior in juvenile control or MS rats nor aggressive behavior in adult control or MS rats. To verify that MS did not alter social approach/social motivation, the absolute time investigating the *same* rat during the acquisition period and the absolute time investigating the *same* + *novel* rat during the discrimination period were measured.

2.4. Implantation of microdialysis probes

For Exp. 2 and 3, juvenile and adult control and MS rats were anesthetized with isoflurane (Forene®, Abbott GmbH & Co. KG, Wiesbaden, Germany), injected with 0.05 ml of an antibiotic substance (Baytril®, Bayer Vital GmbH, Leverkusen,