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Species and individual differences in juvenile female alloparental care are associated with oxytocin receptor density in the striatum and the lateral septum

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Abstract

The neuropeptide oxytocin has been implicated in the regulation of affiliative behavior and maternal responsiveness in several mammalian species. Rodent species vary considerably in the expression of juvenile alloparental behavior. For example, alloparental behavior is spontaneous in juvenile female prairie voles (~20 days of age), takes 1–3 days of pup exposure to develop in juvenile rats, and is nearly absent in juvenile mice and meadow voles. Here, we tested the hypothesis that species differences in pup responsiveness in juvenile rodents are associated with oxytocin receptor (OTR) density in specific brain regions. We found that OTR density in the nucleus accumbens (NA) is highest in juvenile prairie voles, intermediate in juvenile rats, and lowest in juvenile mice and meadow voles. In the caudate putamen (CP), OTR binding was highest in prairie voles, intermediate in rats and meadow voles, and lowest in mice. In contrast, the lateral septum (LS) shows an opposite pattern, with OTR binding being high in mice and meadow voles and low in prairie voles and rats. Thus, alloparental responsiveness in juvenile rodents is positively correlated with OTR density in the NA and CP and negatively correlated with OTR density in the LS. We then investigated whether a similar receptor–behavior relationship exists among juvenile female prairie voles by correlating individual variation in alloparental behavior with variation in OTR density. The time spent adopting crouching postures, the most distinctive component of alloparental behavior in juveniles, was positively correlated with OTR density in the NA ($r = 0.47$) and CP ($r = 0.45$) and negatively correlated with OTR density in the lateral septum ($r = -0.53$). Thus, variation in OTR density in the NA, CP, and LS may underlie both species and individual differences in alloparental care in rodents.

Keywords: Pup aversion; Maternal behavior; Mouse; Rat; Septum; Voles

Oxytocin (OT) is a hypothalamic neuropeptide that has been widely implicated in the regulation of positive social interactions, social bonding, and maternal responsiveness in several mammalian species, ranging from rodents to humans (Carter, 2003; Cho et al., 1999; Fahrbach et al., 1985; Insel, 1992; McCarthy et al., 1992; Keverne and Kendrick, 1992; Kosfeld et al., 2005; Pedersen and Prange, 1979, 1985; Peterson et al., 1991; Uvnas-Moberg, 1998; Witt et al., 1992). Alloparental behavior is displayed by juveniles (~20 days of age) in some, but not all, rodent species. For example, while most juvenile female prairie voles (20 days of age) show an immediate maternal response toward pups, rats require 1–3 days of pup exposure before expressing maternal behavior, and mice or meadow voles (data unpublished) fail to show any maternal responses toward pups (Bridges et al., 1974; Gandelman, 1973; Lonstein and DeVries, 2000; Mayer and Rosenblatt, 1979; Olazábal and Morrell, 2005; Olazábal and Young, 2005; Roberts et al., 1998). Little is known about the neurobiological mechanisms regulating alloparental care.

The neuroanatomical distribution of oxytocin receptors (OTR) in the brain varies extensively across species and it has been proposed that species differences in OTR distribution may underlie species differences in social behavior (Tribollet et al.,

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1992; Young, 1999; Insel and Shapiro, 1992). Oxytocin receptors are present in several brain regions involved in the regulation of maternal behavior, including the nucleus accumbens (NA; Champagne et al., 2004; Hansen et al., 1993; Keer and Stern, 1999; Li and Fleming, 2003a,b; Lonstein et al., 1998; Numan and Insel, 2003), caudate putamen (CP; Felicio et al., 1996), lateral septum (LS; Flannelly et al., 1986; Fleischer and Slotnick, 1978), and medial preoptic area (MPOA; Numan et al., 1977; Numan and Insel, 2003; Rosenblatt and Ceus, 1998). We hypothesized that quantitative difference in OTR binding in these brain regions across species may be related to the species-specific juvenile response to pups.

Comparisons of receptor distributions among species based on earlier separate studies in adults suggest that prairie voles have higher levels of OTR in the striatum than rats, mice, and meadow voles, while the last two species have higher levels of OTR in the LS (Insel, 1992; Tribollet et al., 1992; Young, 1999), although a truly comparative study has not been reported. Furthermore, in rats, there is a developmental decline in OTR binding in the NA (Shapiro and Insel, 1989) that is associated with a decline in responsiveness to pups (Mayer and Rosenblatt, 1979). Therefore, we first compared, in the same assay, OTR binding in 20-day-old juvenile mice, meadow, prairie voles, and rats to determine whether juvenile alloparental behavior is associated with OTR binding in the NA, CP, LS, and MPOA.

Our results confirm that prairie voles, the only species in which juvenile females show spontaneous maternal response, had higher OTR binding in the NA and CP and lower in the LS compared to mice and meadow voles which do not show any maternal response as juveniles. Rats, which show alloparental behavior after a few days of pup exposure, had also lower values in the NA and CP compared to prairie voles. Since relationships between species differences in social behavior and receptor expression patterns may be informative for identifying potential mechanisms underlying individual variation in behavior, we then correlated OTR density in these brain regions with the quality of alloparental behavior displayed by juvenile female prairie voles. We found a similar correlation in each of these brain regions between OTR density and alloparental care among individuals.

Methods

Experiment I

Subjects

Subjects were juvenile (19–22 days of age) female mice (C57BL/6; $n = 7$), meadow voles ($n = 6$), prairie voles ($n = 9$), and rats (Crl:CD (SD), Charles River, $n = 8$). Mice and rats were the first generation from adults purchased from Charles River Laboratories Inc., while meadow and prairie voles were from our colony maintained at the Yerkes Laboratory Animal Facility at Emory University. This facility is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC). All animals were weaned at the age 19–22 days, deeply anesthetized with Isofluorane (Novaplus™; Abbott Laboratories, IL), and decapitated with a guillotine.

Brain tissue collection and radioligand receptor autoradiography

Brains were removed from the skulls, frozen immediately on dry ice, and stored at −80°C until sectioned. Twenty-micrometer-thick frozen brain sections were obtained using a cryostat. Sections collected extended from the olfactory nuclei to the caudal region of the basolateral amygdala and were mounted in Superfrost plus slides (Fisher, Pittsburgh, PA) and stored at −80°C until used.

Slides were processed for receptor autoradiography using a selective ^{125}I-labeled oxytocin receptor ligand, [^{125}I]-ornithine vasotocin analogue (NEN/PerkinElmer, ^{125}I-OVTA, 2200 Ci/mmol) and standard receptor autoradiography procedures reported previously (Lim et al., 2004). Briefly, sections were removed from the freezer and allowed to equilibrate to room temperature and dry for 1 h before the autoradiographic procedures began. Sections were immersed in 0.1% paraformaldehyde in phosphate-buffered saline (pH 7.4) for 2 min at room temperature. Slides were then rinsed twice in Tris–HCl buffer (pH 7.4) and later incubated for 60 min in 50pM ^{125}I-OVTA in Tris buffer with 10 mM $MgCl_2$, 0.1% bovine serum albumin (RIA grade, fraction V, Sigma), and 0.05% bacitracin. Unbound ligand was removed with 4 washes in 50 mM Tris pH 7.4, 10 mM $MgCl_2$. The slides were finally quickly dipped in cold dH_2O and rapidly dried and exposed to BioMax MR film (Kodak, Rochester, NY, USA) along with ^{125}I autoradiographic microscale standards for 48 h (Amersham Biosciences). All slides for each experiment were processed in a single assay.

Data analysis

The analysis of the autoradiography was performed as previously reported (Phelps and Young, 2003). Optical density readings were measured and converted to disintegrations per minute (dpm/milligram tissue equivalent) based on the autoradiographic standards using our automated computer-based image analysis system and AIS™ software version 6.0 (Imaging Research Inc.).

OTR density was measured unilaterally using between 2 and 4 sections depending on the brain region (CPmedial = 4, MPOA = 2, NA (core and shell) = 4, and LS = 4), and the average value was recorded. Specific binding was calculated by subtracting a background value, taken from an adjacent area with no OTR binding, from the value recorded for each region. The dorsal region of the CP was excluded from this study because rats have a dense band of OTR binding not representative of the CP as a whole.

Experiment II

Subjects were 26 juvenile female prairie voles (19–22 days of age) from our colony maintained at the Yerkes Laboratory Animal Facility at Emory University. All animals were weaned at the age 19–22 days, individually housed in cages 28X17X13 cm with transparent Plexiglas Walls under a 12/12-h dark/light cycle and a stable environmental temperature of 22°C with access to food (LabDiet® rabbit) and water ad libitum. Bed-ócobs® Laboratory Animal Bedding (Ohio, USA) was used as bedding material.

Maternal behavior test

Subjects were individually housed in a clean cage and allowed to habituate for 45–90 min before the maternal behavior test began. The maternal behavior test has been previously described (Olazábal and Young, 2005) and will be briefly summarized here. Two pups (2–5 days old) were placed into the cage opposite to where the subject was located. The behaviors scored during the 15 min test included number of approaches and withdrawals from the pups, latency to first approach, time far from pups (more than ~15 cm away), attack of pups, time spent licking and grooming the pups, and time hovering over at least one pup.

At the conclusion of the test, the animals were euthanized, and brains were removed and sectioned as described in the Experiment I. Autoradiographic analysis of OTR in the NA (core and shell), CPmedial, and LS was carried out as described above in Experiment I.

Statistical analysis

Data collected in Experiment I were analyzed using a multiple ANOVA followed by Fisher's post hoc test. In Experiment II, we performed a step-wise multiple regression analysis to identify the brain regions in which OTR density was most useful to predict the dependent variable, which in this case was the time spent hovering over the pups. The step-wise procedure is a mathematical maximization procedure in which the variable

with the highest correlation is entered first, followed by the next predictor with the largest semi-partial correlation, until additional variables no longer improve the correlation. The level of statistical significance was set at 0.05. Data are expressed as means ± SE.

Results

Experiment I

OTR binding in the nucleus accumbens and caudate putamen across species

The ANOVA revealed a significant main effect of species for the shell, $F(3,23) = 7.6$, $P < 0.001$ and core subregions of the NA, $F(3,23) = 12.8$, $P < 0.001$. Post hoc analysis revealed that OTR density in the NA (shell) was higher in prairie voles than in the other three species ($P < 0.5$), intermediate in rats, and low in the meadow voles and mice (Figs. 1, 2). Meadow voles did not differ from mice or rats. Rats had higher OTR binding in the shell subregion of the NA than mice ($P < 0.5$). OTR was also higher in the core region of the NA in prairie voles than in the other three species ($P < 0.1$). The ANOVA also revealed a significant main effect of species for the CPm, $F(3,23) = 8.3$, $P < 0.01$. Prairie voles had higher OTR binding than each of the other groups ($P < 0.1$); meadow voles did not differ from mice or rats, and mice had significantly lower OTR binding than rats ($P < 0.5$; Figs. 1, 2).

OTR binding in the lateral septum and medial preoptic area across species

There was a main effect of species for the lateral septum, $F(3,23) = 14.8$, $P < 0.001$. Post hoc analysis revealed that prairie voles and rats had lower OTR than meadow voles and mice ($P < 0.1$). The OTR binding in the lateral septum did not differ between prairie voles and rats, or between meadow voles and mice (Figs. 1, 2). There was no difference in the OTR binding in the MPOA across all species ($P > 0.70$; meadow voles = 384 ± 132; mice = 327 ± 57; prairie voles = 295 ± 57; rat = 223 ± 30).

Experiment II

Correlation between OTR binding and maternal responses in prairie voles

Most juveniles showed a positive maternal response to pups. Twenty females reached our criteria for displaying maternal

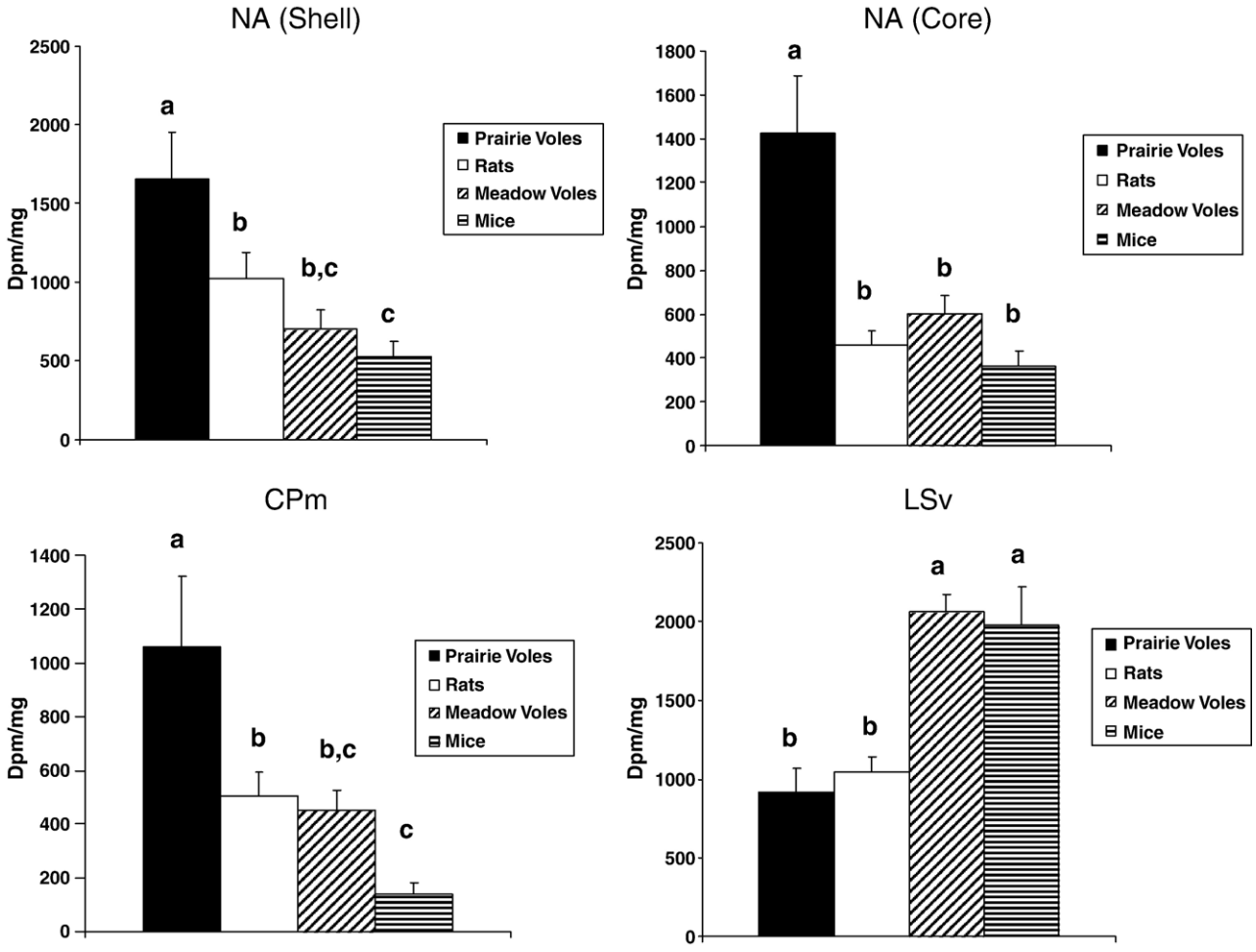

Fig. 1. Graphs illustrating OTR binding density in the nucleus accumbens (NA), the medial part of the caudate putamen (CPm), and the lateral septum (LS) across species. Data are expressed as mean ± SE (groups not sharing a letter differ significantly from each other; $P < 0.05$).

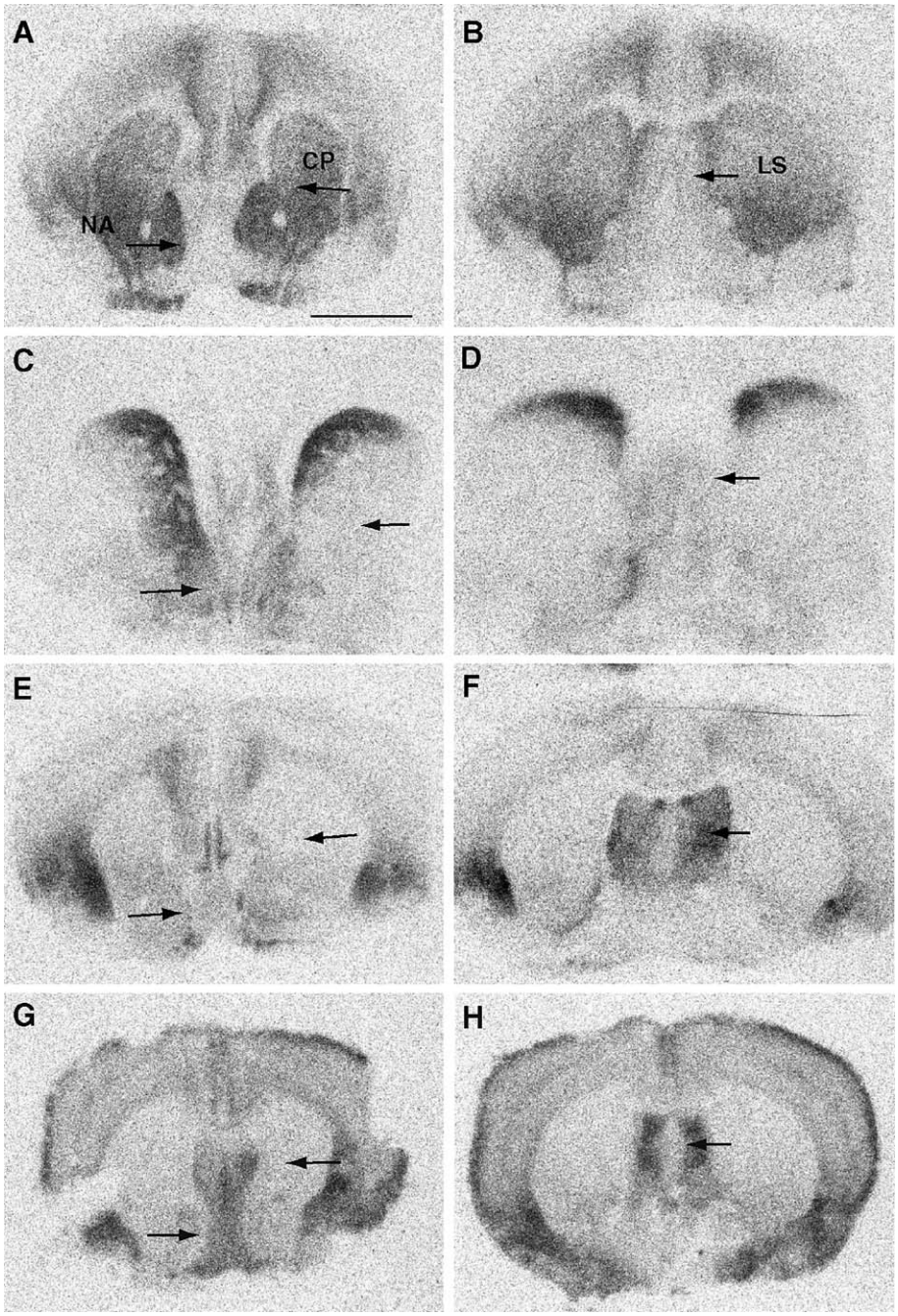

Fig. 2. Autoradiograms of brain sections illustrating the autoradiographic signal for I^{125} OTA binding representative of prairie voles (A, B), rats (C, D), meadow voles (E, F), and mice (G, H). Note that the OTR density is higher in the lateral septum (LS, see arrow) of meadow voles and mice (F, H) than in prairie voles and rats (B, D) and is low in the shell subregion of the nucleus accumbens (NA, see arrow) in meadow voles and mice (E, G) intermediate in rats (C) and highest in prairie voles (A). Scale bar = 2 mm.

behavior (licking more than 5 s and adopting crouching posture for longer than 30 s during the 15-min test), and six females did not. Because hovering over the pups is the most distinctive component of maternal behavior in prairie voles, this variable was analyzed and correlated with OTR density in the NA, CP, and LS. However, because animals that do not show maternal response will obviously show a score of zero for time spent adopting crouching postures, this correlation analysis was repeated excluding these non-maternal animals.

The time that the juveniles spent adopting a crouching posture was positively correlated with OTR binding in the NA (shell/core) and CP (R = 0.46/.47, and R = 0.45 respectively; $P < 0.1$; n = 26; Fig. 3). In contrast, OTR in the LS was negatively correlated with the time adopting a crouching posture ($R = -0.53$; $P < 0.1$). The step-wise procedure indicated that OTR density in the NA and LS were the best predictors of the time crouching over the pups. Multivariate regression analysis for NA (shell) and LS

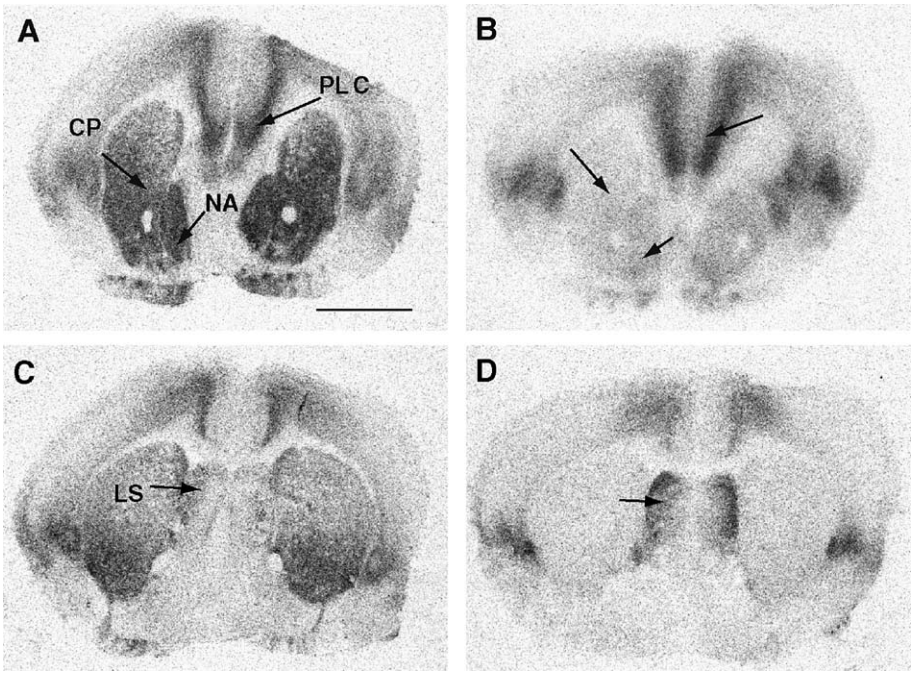

Fig. 3. Autoradiograms of brain sections illustrating the autoradiographic signal for I^{125} OTA for two juvenile prairie voles that showed maternal responses (A, C) or not (B, D). Note that while OTR density in the nucleus accumbens (NA) and the medial region of the caudate putamen (CP) is higher in the maternal than in the non-maternal juvenile example (see arrows A, B), there is no difference in the prelimbic cortex (PLC, see arrows A, B) and is lower in the lateral septum (LS; see arrows C, D). Scale bar = 2 mm.

OTR density as predictors for time spent adopting a crouching posture resulted in an $R = 0.66$, explaining 44% of the variance ($P < 0.01$). OTR binding in the NA (shell/core) was positively correlated with binding in the CP ($R = 0.89/.88$; $P < 0.001$; Fig. 4), but there was no correlation between the NA (shell/core) and the LS ($R = 0.08/.08$; $P > 0.65$).

When only the animals that reached our criteria for displaying maternal behavior are included in the correlation, the relationship between time spent adopting crouching posture and OTR binding in the NA (shell/core) and CP is even higher than when all animals are included ($R = 0.69/0.69$; and $R = 0.66$ respectively; $P < 0.01$; Fig. 5). However, the correlation between the time spent adopting a crouching posture and the OTR binding in the LS became non-significant ($R = 0.24$; $P < 0.31$). A t test comparison revealed a significant difference in the binding for OTR in the LS of maternal (3251 ± 178) and non-maternal (4501 ± 225) juvenile females ($P < 0.02$). However, this result should be considered carefully due to the imbalance between the number of animals that showed maternal responses and those that did not (20 and 6 respectively). Thus, OTR density in the LS may be a better predictor of the presence or absence of alloparental care, while the NA and CP may be better predictors of the quality of alloparental care.

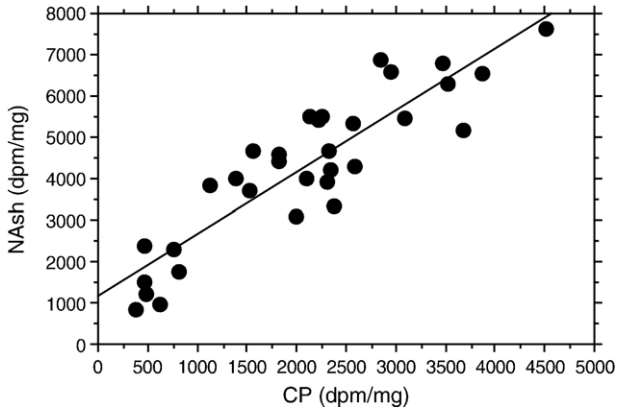

Fig. 4. Scattergram illustrating the relationship (Pearson $R = 0.89$) between OTR binding in the nucleus accumbens (shell; NAsh) and the medial part of the caudate putamen (CP).

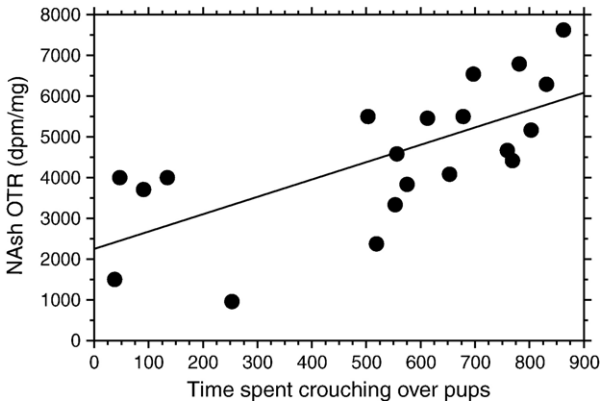

Fig. 5. Scattergram illustrating the relationship (Pearson $R = 0.69$) between OTR binding in the nucleus accumbens (shell; NAsh) and the time spent adopting crouching posture.

Discussion

Species differences in the distribution of OTR in the rodent brain have been proposed to underlie species differences in the social behavior (Insel and Shapiro, 1992; Young, 1999). In this study, we compared alloparental behavior of juvenile females of 4 different rodent species (meadow voles, mice, prairie voles, and rats) with their OTR binding density in the NA, CP, LS, and MPOA. We found that higher density of OTR in the NA and CP was associated with higher levels of alloparental behavior across species. In contrast, the opposite relationship was found for OTR binding in the LS. Juvenile female prairie voles, the only group that shows spontaneous maternal behavior at age 20 days, had the highest OTR binding in the NA and the CP and low binding in the LS. When OTR binding in the NA, CP, and LS was correlated with the maternal response displayed by individual female juvenile prairie voles, we found that higher quality of alloparental behavior was also positively correlated to OTR density in the NA and CP and negatively correlated to OTR density in the LS.

There is evidence that the NA is involved in regulating maternal responses and the processing of pup-related stimuli (Champagne et al., 2004; Hansen et al., 1993; Keer and Stern, 1999; Li and Fleming, 2003a,b; Lonstein et al., 1998; Numan and Insel, 2003; Numan et al., 2005; Olazábal and Morrell, 2005). However, the precise nature of this regulation and the specific behavioral components regulated are not yet clear. Our results suggest than increased OT neurotransmission in the NA should facilitate alloparental care. However, it must be emphasized that the results of the present study are correlational and require follow-up pharmacological studies to confirm a causal relationship. Unfortunately, pharmacological manipulations in juvenile prairie voles are difficult due to the small size and weight of 20 day old prairie voles (~10 g). However, we have recently found that spontaneously maternal adult female prairie voles also have higher OTR binding in the NA than non-maternal females, and that OT antagonist infused into the NA blocks adult spontaneous maternal responses (Olazabal and Young, submitted). OT neurotransmission in the NA could facilitate maternal behavior via a number of mechanisms, including increased exploratory behavior, reduced response to novel stimuli, or increased attractive value of pups or social stimuli. Further studies are needed to determine the mechanism by which OT acting in the NA facilitates maternal responses.

There is only one study suggesting that the CP may be involved in learning maternal experiences in rats (Felicio et al., 1996). The CP has been more generally implicated in the control of motor movement, exploration, and motivation (Graybiel et al., 1994). Several studies show that hyperactivity can be induced by dopaminergic manipulation in this brain region (Maruya et al., 2003; Zhang et al., 2001). Whether OT and dopamine interact in the striatum is unclear, but OT may alter general motivation, locomotor, or exploratory activity in juvenile prairie voles, affecting the response to pups among other social or behavioral responses. However, it should be noted that OTR in NA and CP are highly correlated with each other in prairie voles, therefore, it is possible that only one of these brain regions is involved in regulating maternal responses.

Another intriguing finding in this study was the negative correlation between OTR density in the LS of prairie voles and juvenile alloparental behavior. This was an unexpected result but relevant to the understanding of OT function in various regions throughout the brain. The positive and negative relationship between NA/CP and LS OTR density, respectively, and alloparental behavior, suggests that these brain regions may play opposite roles in the neural circuit that supports juvenile female maternal response. This supports the hypothesis that OT differentially modulates maternal or other social behaviors by acting at different levels of the social neural circuit. In addition, although OTR in LS was negatively related to juvenile alloparental behavior, we cannot exclude the possibility that OT in this brain region facilitates maternal behavior in adults, around parturition or in other species such as rat, mice, or meadow voles that show completely different OTR distribution.

The MPOA is a principal component of the neural circuit that regulates maternal behavior (Numan et al., 1977; Numan and Insel, 2003; Rosenblatt and Ceus, 1998). Although OT facilitation of alloparental behavior through the MPOA cannot be excluded, our results suggest that the variability in OTR binding in the MPOA across or within species does not contribute to the variability in spontaneous or sensitized maternal behavior, as also shown in adult rats by Francis et al. (2000, 2002).

The factors that contribute to the striking differences in OTR expression and distribution across species or between individuals of the same species are unknown but may include differences in cis-regulatory elements located near the gene, differences in transcription factors, early environmental experiences, and hormonal influences. Several laboratories are currently studying these possibilities (Francis et al., 2002; Gimpl and Fahrenholz, 2001; Hammock and Young, 2005; Pedersen and Boccia, 2002; Young et al., 1997; Young and Gainer, 2003). In summary, this is the first study, to our knowledge, in which species differences in brain–behavior relationships have been used to identify potential neural mechanisms underlying individual variation in social behavior. This study further strengthens the hypothesis that plasticity in neuropeptide receptor systems contributes to the diversity in social behavioral phenotypes, both between species and among individuals of the same species.

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