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Dopamine, oxytocin, and vasopressin receptor binding in the medial prefrontal cortex of monogamous and promiscuous voles

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Abstract

Comparisons between monogamous and promiscuous vole species have proven useful in examining neurobiological mechanisms underlying social attachment. Reward processing is important for social attachment, and the medial prefrontal cortex (mPFC) exerts a direct influence on reward pathways. Dopamine (DA), oxytocin (OT), and arginine vasopressin (AVP) all have been implicated in the regulation of social attachment in monogamous voles. Therefore, we used radiolabeled ligands to examine dopamine D_1- and D_2-like, OT, and AVP V_{1a} receptor binding densities in the mPFC of monogamous and promiscuous voles. Species differences were found; monogamous voles had higher densities of D_2-like and OT receptor binding and lower densities of D_1-like and V_{1a} receptor binding than did promiscuous voles. Sex differences also were found; females had higher densities of OT receptor binding but lower densities of V_{1a} receptor binding than did males in both species. Further, the laminar distribution of receptor binding indicates the possibility of an interaction between DA and OT systems in the mPFC in the regulation of social attachment. Differences in D_1- and D_2-like receptor binding between species are discussed in terms of how they might modulate cortical activity and subsequent DA release in the nucleus accumbens (NAcc).

Keywords: Dopamine; Neuropeptides; Receptors; mPFC; Monogamy

Social attachments are a vital part of healthy human behavior and an inability to form such attachments is regarded as a symptom of mental disorders such as schizophrenia and autism. Studying the mechanisms underlying social attachment requires a model animal that displays behaviors similar to what is seen in human social attachment. Since traditional laboratory animals such as rats and mice do not display the requisite behaviors, prairie voles (*Microtus ochrogaster*) have become an important model for the study of the neurobiology of social attachment [5,17,38,46]. Prairie voles are monogamous and form life-long breeding pairs in which both sexes occupy a common nest, guard against intruders, and retrieve and care for pups [10]. Other vole species, such as montane (*Microtus montanus*) and meadow voles (*Microtus pennsylvanicus*), display different life strategies and social behaviors. These species are promiscuous, display low levels of social affiliation, do not selectively mate with one partner, and only the female cares for pups [9,18,25]. Thus, voles serve as an excellent comparative model, and comparisons between monogamous and promiscuous vole species have yielded significant insights into the neurobiology of social attachment [8,15,16,20,41,42].

Central dopamine (DA) is important for the formation of attachments between adult male and female prairie voles (pair bonding) [1,12,39]. Dopaminergic cells in the ventral tegmental area (VTA) project both to the nucleus accumbens (NAcc) and the medial prefrontal cortex (mPFC) [22,32]. In turn, the mPFC sends glutamatergic projections back to the VTA and to the NAcc [3,4]. Dopamine in the mPFC modulates the activity of glutamatergic projections to NAcc to regulate local DA release [19,34]. Since DA release in the NAcc is important for pair bonding in prairie voles [1,12,24], DA receptors in the mPFC may play a role in this process. Therefore, the first part of the present study was designed to compare the distributions of D_1- and D_2-like DA receptors in the mPFC of monogamous and promiscuous vole species.

The neuropeptides oxytocin (OT) and arginine vasopressin (AVP) also are involved in pair bonding [7,13,23,43,44]. The central distributions of OT and AVP V_{1a} receptors differ between monogamous and promiscuous voles [15,16,42]. Further, the impact of these neuropeptide systems on pair bonding differs

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between sexes in monogamous voles: females are more sensitive to OT whereas males are more sensitive to AVP [7,13,44]. Importantly, microinjection of an OT receptor antagonist into the mPFC alters pair bond formation in female prairie voles [45]. Although untested in the mPFC, AVP manipulations in the lateral septum and ventral pallidum are known to alter pair bonding in male voles [20,21,23]. Therefore, in the second part of the present study, we assessed OT and AVP V_{1a} receptor distributions in the mPFC of monogamous and promiscuous voles. In both the DA and neuropeptide experiments, males and females were included to examine potential sex differences in receptor binding. We hypothesized that DA/OT/AVP receptor distributions in the mPFC differ between monogamous and promiscuous voles, and that such differences may contribute to species-specific social attachment behavior.

Subjects were sexually naive adult male and female prairie, meadow, and montane voles from captive breeding colonies. All animals were weaned at 21 days of age, and were housed in same-sex sibling groups (2–3/cage) in plastic cages (20 cm × 50 cm × 40 cm) under a 14 h light/10 h dark cycle with lights on at 07:00 h. Temperature was maintained at about 20 °C. Food and water were provided ad libitum. All experimental procedures were in accordance with National Institutes of Health guidelines, and were approved by the Florida State University Animal Care and Use Committee.

The first part of this study was designed to examine DA receptor binding in the mPFC of monogamous and promiscuous voles. At about 3 months of age, sexually naive prairie and meadow vole subjects were anesthetized with sodium pentobarbital (1 mg/10 g body weight) and decapitated. Brains were removed and frozen on dry ice, then cut into 15 μm coronal sections on a cryostat and thaw-mounted onto Superfrost/Plus slides (Fisher). Sections were stored at −80 °C until processed for DA receptor autoradiographic binding.

The second part of this study was to examine OT and AVP V_{1a} receptor binding in the mPFC of monogamous and promiscuous voles. These data were obtained from autoradiographs processed in previous studies [41,42]. Those experiments focused on the ontogenetic patterns of OT and AVP V_{1a} receptor binding in selected brain regions in prairie and montane voles, and detailed analyses of the mPFC were not performed.

For DA receptor binding, adjacent brain sections at 90 μm intervals were rinsed in 50 mM Tris–HCl (pH 7.4) 2 min × 10 min and then incubated in the same buffer with 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$ and 50 pM ^{125}I-SCH23982 (for D_1-like receptors) or ^{125}I-2′-iodospiperone (for D_2-like receptors) (Perkin-Elmer, MA). Fifty nM ketanserin (RBI, MA) was added to prevent binding to 5-HT_2 receptors. After 45 min (D_1) or 90 min (D_2) incubations at room temperature, sections were rinsed in fresh ice-cold buffer containing 0.1% paraformaldyhyde and then twice in ice-cold buffer for 5 min, followed by immersion in buffer for 60 min with gentle stirring. Finally, sections were rinsed in ice-cold ddH_2O and dried under a stream of cool air. Nonspecific binding was defined by pretreating adjacent sections with SCH23390 or eticlopride prior to incubation in the buffer containing ^{125}I-SCH23982 or ^{125}I-2′-iodospiperone, respectively. Slides were exposed to BioMax MR film for approximately 4 h.

Detailed procedures for OT and AVP V_{1a} receptor binding were described previously [41,42]. OT or AVP V_{1a} receptor binding was processed by using 50 pM ^{125}I-OTA or ^{125}I-linear-AVP (Perkin-Elmer, MA), respectively. Non-specific binding was defined by pretreating adjacent sections with the selective OT antagonist, [Thr^4Gly^7]OT (1 μM), followed by incubation in the buffer containing ^{125}I-OTA, or with the V_{1a} ligand, $d(CH_2)_5$[Tyr(Me)]AVP (1 μM), followed by incubation with ^{125}I-linear-AVP [41,42].

The autoradiographs were analyzed for the densities of D_1- and D_2-like DA receptor and OT and AVP V_{1a} receptor binding in the mPFC using the NIH IMAGE program. Sections were anatomically matched between subjects, and individual means for each subject were obtained by measuring grain density bilaterally in four sections from the mPFC. The background density was subtracted from the measurement of each section. Data for each receptor type were analyzed by a two-way analysis of variance (ANOVA, species-by-sex), followed by a Student–Newman–Keuls (SNK) posthoc test when significant main effects were found.

Specific binding in mPFC was found for all four receptor types. D_1-like receptors appeared to be concentrated in deep layers of the cortex (Fig. 1A and B), while D_2-like receptors were more evenly distributed throughout all layers of the cortex (Fig. 1D and E). While anatomical distribution patterns of each type of DA receptor binding appeared similar in both species, the densities of DA receptor binding in mPFC differed between species. Prairie voles had lower densities of D_1-like receptor binding ($F_{1,19} = 10.9$, $p < 0.01$; Fig. 1C) and higher densities of D_2-like receptor binding ($F_{1,18} = 13.9$, $p < 0.01$; Fig. 1F) than did meadow voles. No main sex differences were detected for either type of DA receptor in the mPFC. However, a species-by-sex interaction was found for D_1-like receptor binding, in which male prairie voles had a lower density of D_1-like receptor binding than did all other groups ($F_{1,19} = 7.9$, $p < 0.01$; Fig. 1C). A species-by-sex interaction was not found for the density of D_2-like receptor binding in mPFC.

OT receptor binding appeared to be highest in the deep layers of mPFC in both vole species (Fig. 2A and B). Prairie voles had higher densities of OT receptor binding than did montane voles ($F_{1,16} = 29.5$, $p < 0.001$; Fig. 2C). A sex difference was also found; females had higher densities of OT receptor binding than did males ($F_{1,16} = 40.4$, $p < 0.001$; Fig. 2C). Further, AVP V_{1a} receptor binding appeared to be mainly concentrated in superficial layers of mPFC in both species (Fig. 2D and E). Densities of V_{1a} receptor binding in mPFC were higher in montane than in prairie voles ($F_{1,16} = 38.6$, $p < 0.001$), and were higher in males than in females ($F_{1,16} = 14.2$, $p < 0.01$; Fig. 2F). No species-by-sex interaction was found for either OT or AVP V_{1a} receptor binding in the mPFC.

The present study was conducted to compare the dopamine D_1- and D_2-like, OT, and AVP V_{1a} receptor binding in the mPFC between males and females of vole species with different life strategies and social behaviors. We found differences in the regional densities and distribution patterns of each type of

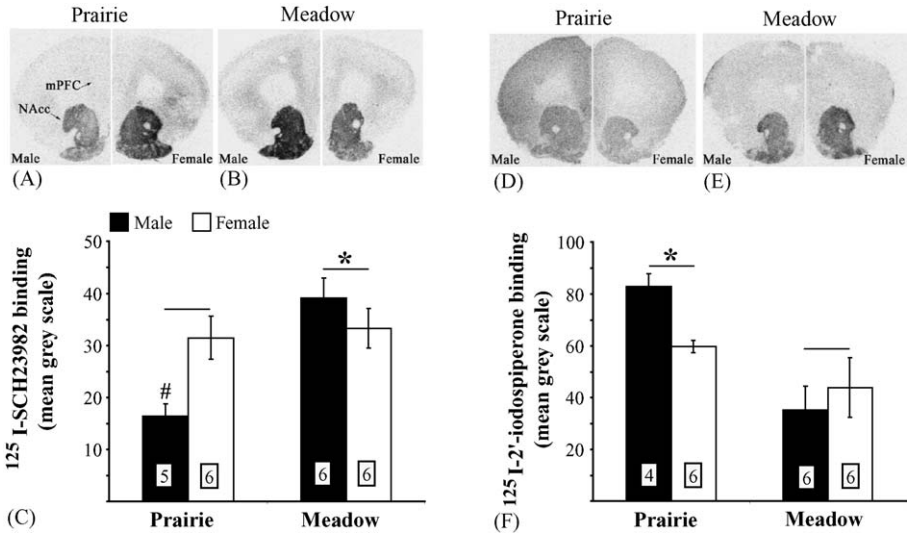

Fig. 1. Species and sex differences in D_1- (A–C) and D_2-like (D–F) dopamine receptor binding in the mPFC. Each photoimage is composed with male on the left and female on the right. Prairie voles had less D_1-like and more D_2-like receptor binding than did meadow voles. Further, male prairie voles had the lowest density of D_1-like receptor binding in mPFC than did any other groups. Data are presented as mean ± S.E.M. (*) species differences; (#) sex difference within each species; mPFC: medial prefrontal cortex; NAcc: nucleus accumbens. Group sizes are shown within each bar.

receptors in the mPFC between monogamous and promiscuous voles. In addition, sex differences also were found, particularly for OT and AVP receptor binding in mPFC. It should be noted that social behaviors were not tested on the animals used in the present study because extensive data have amply demonstrated that these species show different social behaviors, including mating-induced pair bonding, selective aggression, and parental care [14,25,26,38,44,46], which served as a foundation for formation of our hypothesis. Furthermore, displaying social behaviors may cause changes in receptor densities of the DA/OT/AVP systems that are involved in the regulation of those social behaviors. As such we chose not to pre-screen animals for specific behavioral characteristics and instead relied on an extensive literature showing that the majority of individuals in each species display species-specific behaviors. We feel that the inclusion of randomly chosen sexually naive animals provides a better indication of within-species variability, and, as such, makes the analyses more conservative.

One drawback of the present study is the use of two promiscuous species; meadow voles were used in the DA receptor binding experiment whereas montane voles were used in the neuropeptide receptor binding experiment that was previously conducted. This discrepancy was due to the fact that we no longer have a montane vole colony for the DA receptor binding experiment and that we did not feel justified to sacrifice another 20 or more animals for the neuropeptide receptor binding experiment as the

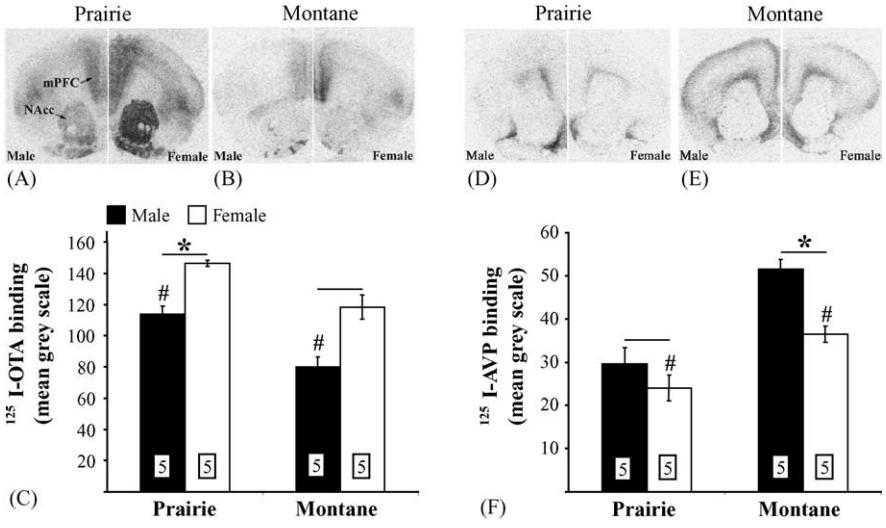

Fig. 2. Species and sex differences in oxytocin (A–C) and vasopressin V_{1a} (D–F) receptor binding in the mPFC. Each photoimage is composed with male on the left and female on the right. Oxytocin receptor binding was higher in prairie than in montane voles and higher in females than in males. Vasopressin receptor binding was higher in montane than in prairie voles and higher in males than in females. Data are presented as mean ± S.E.M. (*) species differences; (#) sex difference within each species; mPFC: medial prefrontal cortex; NAcc: nucleus accumbens. Group sizes are shown within each bar.

autoradiographs were available from the previous studies. Both montane and meadow voles are promiscuous and display similar social behaviors [6,38,40], and importantly, the two show similar distribution patterns of the OT and AVP V_{1a} receptor binding that differ from those in monogamous voles [15,16]. However, as we cannot exclude a possibility that differences in the DA/OT/AVP receptor binding in the mPFC are species-specific, caution will need to be taken for data interpretation.

In rats, D_1- and D_2-like DA receptors are mostly located in cortical layers V and VI [30,36], and these layers contain the most DAergic terminals [29,35]. We found similar laminar distributions of D_1-like receptors in both species, which were noticeably concentrated in deep layers of the cortex, while D_2-like receptors seemed to be more evenly distributed throughout all layers in both species.

Monogamous voles had lower D_1- and higher D_2-like receptor binding in the mPFC than did promiscuous voles. This species difference may reflect an adaptation in the mPFC associated with a monogamous life strategy. The cell population in the mPFC consists of mostly glutamatergic excitatory projection neurons and GABAergic inhibitory interneurons, typically identified as pyramidal or nonpyramidal neurons, respectively [27]. In the rat, D_1-like receptors are found almost exclusively on nonpyramidal neurons, while D_2-like receptors are found in both small pyramidal and large nonpyramidal neurons, and both subtypes may also be colocalized on nonpyramidal neurons [37]. Because D_1-like receptors are coupled to stimulatory G-proteins, activation of these receptors on GABAergic interneurons ultimately would result in inhibition of excitatory efferents. Activation of D_2-like receptors, which are coupled to inhibitory G-proteins, could disinhibit excitatory efferents if located on GABAergic interneurons, or directly inhibit efferents if located on pyramidal neurons. Stimulation of DA receptors in the mPFC of rats after VTA stimulation or by local application of DA typically results in inhibition of mPFC neurons [19,28,30].

Taking into consideration that pair bond formation in prairie voles depends upon DA release in the NAcc [1,12,24] and that accumbal DA release induced by mPFC stimulation depends upon activation of glutamate receptors in the VTA and NAcc [33,34], it would seem that inhibition of mPFC efferent neurons would be unfavorable for pair bond formation. Therefore, presence of fewer D_1-like and more D_2-like receptors in the prairie vole's mPFC could reflect a modification of receptor compliments on GABAergic interneurons. An increase in the number of D_2-like receptors on these neurons would increase the likelihood that they would be inhibited in response to DA release, and a decrease in D_1-like receptors would decrease the likelihood that they would be excited by DA release. Reducing the excitability of these neurons would increase activity in mPFC efferents. Another possibility is that fewer D_1-like receptors on GABAergic interneurons result in less activation by accumulated extrasynaptic levels of DA. As most cortical D_1-like receptors are located extrasynaptically [31], firing of DAergic cells in the VTA in response to a novel mate could produce an environment in which GABAergic interneurons are more excitable, thus reducing the activity of pyramidal outputs. Lowered excitability of these interneurons in such a situation would be advantageous to an animal that requires glutamatergic input from the mPFC during pair bond formation. Estrogen's ability to increase accumbal DA release [2], however, could negate the need for fewer D_1-type receptors in females, and could explain why female prairie voles do not share the low density of D_1-like receptors with male prairie voles. A complete understanding of the species- and sex-differences in DA receptors will require further study of the cellular localization of DA receptors in the mPFC, as well as of the effects of DA receptor subtype specific pharmacological manipulations on social attachment in prairie voles.

There were striking inverse distributions of OT and V_{1a} receptors, with the former found primarily in deep layers and the latter in superficial layers of cortex without much overlap between the two. The higher density of OT receptor binding in the mPFC in monogamous voles compared to that in promiscuous voles is consistent with findings in a previous study [15]. An interesting finding in the current study is that female voles had higher densities of OT receptor binding in mPFC than did male voles. This finding correlates well with data from past studies showing that female voles are more sensitive to OT effects than are males [13]. Although yet to be determined in voles, sex differences in OT receptor binding likely reflect the influence of sex steroids on the expression of these receptors [11]. While the mechanism through which OT affects neurons in the mPFC remains unknown, blockade of OT receptors in the mPFC indeed blocked female prairie voles' pair bonding behavior [45]. Therefore, anatomical and pharmacological data together suggest that OT in the mPFC may play a role in social attachment.

While the higher density of V_{1a} receptor binding in the mPFC of promiscuous voles is a novel finding, it is consistent with the species-specific densities of this receptor in many other brain areas of voles [16,41,42]. Furthermore, the presence of more V_{1a} receptors in males than in females would be consistent with past findings indicating that males are more sensitive to AVP than are females [44,47]. To date, no pharmacological manipulations of V_{1a} receptors in the mPFC of voles have been carried out, however, due to the relative low density of these receptors in the mPFC of prairie voles and their absence in the layers of the cortex that receive DAergic input, it is possible that the AVP system in the mPFC plays little, if any, role in social attachment.

Our current study has shown that D_1-like DA and OT receptors seem to be most concentrated in deep layers of the cortex in voles. Although the types of neurons that express DA and/or OT receptors are still unknown, these two receptor systems may interact in the regulation of social attachment. An earlier study manipulating OT and DA receptors in another part of the mesocorticolimbic circuit, the NAcc, has shown that OT or a D_2-like receptor agonist injected into the NAcc induces pair bonding in female prairie voles. Furthermore, pair bonding induced either by mating or by activation of OT or DA receptors can be abolished by administration of either an OT or a D_2-like receptor antagonist [24]. These data suggest the necessity of concurrent involvement of both OT and DA systems in the NAcc during pair bonding in voles. However, similar pharmacological manipulations of these receptors in the mPFC need to be conducted to

confirm an interaction between DA and OT in the regulation of social attachment.

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