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NEUROANATOMICAL DISTRIBUTION OF OXYTOCIN AND VASOPRESSIN 1a RECEPTORS IN THE SOCIALLY MONOGAMOUS COPPERY TITI MONKEY (*CALLICEBUS CUPREUS*)

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Abstract—The coppery titi monkey (*Callicebus cupreus*) is a socially monogamous New World primate that has been studied in the field and the laboratory to investigate the behavioral neuroendocrinology of primate pair bonding and parental care. Arginine vasopressin has been shown to influence male titi monkey pair-bonding behavior, and studies are currently underway to examine the effects of oxytocin on titi monkey behavior and physiology. Here, we use receptor autoradiography to identify the distribution of arginine vasopressin 1a receptor (AVPR1a) and oxytocin receptors (OXTR) in hemispheres of titi monkey brain ($n = 5$). AVPR1a are diffuse and widespread throughout the brain, but the OXTR distribution is much more limited, with the densest binding being in the hippocampal formation (dentate gyrus, CA1 field) and the presubiculum (layers I and III). Moderate OXTR binding was detected in the nucleus basalis of Meynert, pulvinar, superior colliculus, layer 4C of primary visual cortex, periaqueductal gray (PAG), pontine gray, nucleus prepositus, and spinal trigeminal nucleus. *OXTR* mRNA overlapped with OXTR radioligand binding, confirming that the radioligand was detecting OXTR protein. AVPR1a binding is present throughout the cortex, especially in cingulate, insular, and occipital cortices, as well as in the caudate, putamen, nucleus accumbens, central amygdala, endopiriform nucleus, hippocampus (CA4 field), globus pallidus, lateral geniculate nucleus, infundibulum, habenula, PAG, substantia nigra, olivary nucleus, hypoglossal nucleus, and cerebellum. Furthermore, we show that, in the titi monkey brain, the OXTR antagonist ALS-II-69 is highly selective for OXTR and that the AVPR1a antagonist SR49059 is highly selective for AVPR1a. Based on these results and the fact that both ALS-II-69 and SR49059 are non-peptide, small-molecule antagonists that should be capable of crossing the blood–brain barrier, these two compounds emerge as excellent candidates for the pharmacological manipulation of OXTR and AVPR1a in future behavioral experiments in titi monkeys and other primate species. **© 2014 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: neuropeptides, receptor binding, nonhuman primate, neuroanatomy, monogamy, pair bonding.

INTRODUCTION

In the last several decades, the neuropeptides oxytocin (OT) and arginine vasopressin (AVP) have emerged as important modulators of social behavior in mammalian species ranging from rodents to sheep to humans (Donaldson and Young, 2008; Freeman and Young, 2013). These molecules are capable of influencing a range of social behaviors including, but not limited to, parental care (Pedersen and Prange, 1979; Pedersen et al., 1982, 2006; Wang et al., 1994), territoriality and aggression (Ferris et al., 1984, 1985; Albers et al., 1986; Albers, 2012; Bosch, 2013), affiliation and social attachment (Winslow et al., 1993; Williams et al., 1994; Young et al., 1999a; Lim and Young, 2006), and social recognition memory (Ferguson et al., 2000, 2001; Bielsky et al., 2005; Skuse et al., 2013). These neuropeptides have been extensively studied in the socially monogamous rodent, the prairie vole (*Microtus ochrogaster*), and both peptides play a critical role in pair bond formation between opposite sex adult mates (Cho et al., 1999; Young and Wang, 2004).

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Abbreviations: ^{125}I-LVA, ^{125}I-linear vasopressin-1a antagonist; ^{125}I-OVTA, ^{125}I-ornithine vasotocin analog; AChE, acetylcholinesterase; AVP, arginine vasopressin; AVPR1a, vasopressin 1a receptor; CA1, CA1 field of the hippocampus; CA4, CA4 field of the hippocampus; Cd, caudate nucleus; CeA, central amygdala; DG, dentate gyrus of the hippocampus; GP, globus pallidus; Hipp, hippocampal formation; LG, lateral geniculate nucleus of the thalamus; LS, lateral septum; NAcc, nucleus accumbens; NBM, nucleus basalis of Meynert; NP, nucleus prepositus; OBD, optical binding density; OT, oxytocin; OXTR, oxytocin receptor; PAG, periaqueductal gray; PG, pontine gray; PSB, presubiculum; Pu, putamen; Pv, pulvinar; SC, superior colliculus; Sp5, spinal trigeminal nucleus; SN, substantia nigra; SuG, superficial gray layer of the superior colliculus; V1, 4C, layer 4C of the primary visual cortex; V1, 5-6, layers 5 and 6 of the primary visual cortex; V2, secondary visual cortex.

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OT and AVP may play similar roles in modulating pair bonding and social attachment in socially monogamous primate species as they do in monogamous rodents. The coppery titi monkey (*Callicebus cupreus*) is a monogamous New World primate known for the selective attachment that develops after mating between male and female partners, who spend extended time in side by side contact, often with their tails twined (Mendoza and Mason, 1986; Mason and Mendoza, 1998). Male titi monkeys treated intranasally with AVP increased contact time with their pair-mate compared to a stranger female (Jarcho et al., 2011). In another socially monogamous primate, the black-penciled marmoset (*Callithrix pencillata*), treatment with OT increased pair-mate huddling, and treatment with an OT receptor (OXTR) antagonist decreased proximity and food sharing between pair-mates (Smith et al., 2010). These studies indicate that OT and AVP can influence species-specific, pair-bond-related behaviors in socially monogamous primates.

While behavioral pharmacology has been useful in demonstrating that OT and AVP can modulate pair bonding and related behaviors in primates, the brain mechanisms by which these peptides modulate pair bonding behaviors are unclear. Identifying the locations of the receptors for OT and AVP in the brain can provide insights into the neural circuits modulated by these peptides to effect species-specific social behaviors. The most commonly used technique for localizing OXTR and the vasopressin 1a receptor (AVPR1a) is receptor autoradiography. This technique has been successfully used to determine the neuroanatomical distribution of OXTR and AVPR1a in several species of rodent, ultimately leading to the identification of brain regions involved in modulating social behavior (Ferguson et al., 2001; Lim and Young, 2004; Lim et al., 2004a,b; Bielsky et al., 2005; Gobrogge et al., 2009). One of the most interesting characteristics of the OXTR and AVPR1a system is the diversity of expression patterns, even among closely related species. For example, the highly social monogamous prairie vole and the relatively asocial, promiscuously breeding meadow vole have dramatically different distributions of each receptor in the brain, and these species differences in receptor distribution are associated with species differences in mating strategies (Insel and Shapiro, 1992; Lim et al., 2004a).

Despite the extensive work done in rodents to map these receptors, the distributions of OXTR and AVPR1a in the brains of primate species are still being discovered. This limitation is due, in part, to the pharmacological profiles of the two commercially available radioligands used for receptor autoradiography: the OXTR radioligand ^{125}I-ornithine vasotocin analog (^{125}I-OVTA) and the AVPR1a radioligand ^{125}I-linear vasopressin-1a antagonist (^{125}I-LVA). While these two radioligands are highly selective for the respective receptors in rodent tissue, they are less selective for primate receptors and exhibit a high, subnanomolar affinity for both OXTR and AVPR1a in human and rhesus macaque tissue (Freeman et al., 2014; Manning et al., 2012). Consequently each radioligand binds to both OXTR and AVPR1a, making it difficult to discriminate with confidence the distribution of the two receptors. This lack of selectivity of the radioligands for the primate receptors brings into question the specificity of the receptor binding results in earlier OXTR and AVPR1a mapping studies in human (Loup et al., 1989, 1991) and rhesus macaque (*Macaca mulatta*) brain tissue (Toloczko et al., 1997).

These issues also highlight the importance of overcoming the promiscuous binding profile of the radioligands in primate tissue by using a competitive binding design. This approach involves co-incubating the tissue with the radioligand and a selective, unlabeled competitor to displace the radioligand from one receptor and reveal the localization of only the receptor of interest. Thus, the goals of the current study were to (i) map the distributions of OXTR and AVPR1a in the brain of the socially monogamous coppery titi monkey using a pharmacologically optimized competitive binding receptor autoradiography protocol previously validated in the rhesus macaque (Freeman et al., 2014), and (ii) to determine the selectivity profile for two antagonists that may be useful in future behavioral pharmacology studies. Due to the particular lack of specificity for the OXTR radioligand when used in the macaque brain (Toloczko et al., 1997; Freeman et al., 2014), we also used *in situ* hybridization to confirm *OXTR* mRNA expression patterns in adjacent tissue sections.

EXPERIMENTAL PROCEDURES

Animals

Animals were housed at the California National Primate Research Center in cages (1.2 m × 1.2 m × 2.1 m) and were on a 12:12 light:dark cycle with lights on at 0600 h and lights off at 1800 h. Temperature was maintained at 21 °C. Housing conditions are identical to what has been previously described (Valeggia and Mendoza, 1999). Animals were fed a diet of monkey chow, banana, marmoset jelly, cottage cheese, apple, and carrot at 0800 h and 1300 h. Animals were euthanized on veterinary advice due to health reasons, none of which included a neurological component, and brains were harvested opportunistically. Two males (aged 6.97 and 5.21 years) and three females (ages: 4.28, 4.33, and 18.81 years) were used for the study. All animals were in stable, long-term pair bonds, and the females had all previously had infants; the males had not previously reproduced. All animal procedures were approved by the University of California, Davis Institutional Animal Care and Use Committee and adhered to the legal requirements for non-human primate research in the United States.

Tissue preparation

Titi monkey brains were removed promptly after death, rinsed with phosphate-buffered saline (PBS), and cut into two hemispheres. The hemispheres were blocked coronally, allowed to freeze completely on dry ice, and placed at −80 °C until sectioning. Hemisphere blocks were removed from −80 °C and brought up to −20 °C

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