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Polymorphism and Genetic Mapping of the Human Oxytocin Receptor Gene on Chromosome 3

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Centrally administered oxytocin has been reported to facilitate affiliative and social behaviours, in functional harmony with its well-known peripheral effects on uterine contraction and milk ejection. The biological effects of oxytocin could be perturbed by mutations occurring in the sequence of the oxytocin receptor gene, and it would be of interest to establish the position of this gene on the human linkage map. Therefore we identified a polymorphism at the human oxytocin receptor gene. A portion of the 3′ untranslated region containing a 30 bp CA repeat was amplified by polymerase chain reaction (PCR), revealing a polymorphism with two alleles occurring with frequencies of 0.77 and 0.23 in a sample of Caucasian CEPH parents (n = 70). The CA repeat polymorphism we detected was used to map the the human oxytocin receptor to chromosome 3p25-3p26, in a region which contains several important genes, including loci for Von Hippel-Lindau disease (VHL) and renal cell carcinoma. © 1995 Wiley-Liss, Inc.

KEY WORDS: CA repeats, affiliative behaviors, VHL

INTRODUCTION

Oxytocin is a phylogenetically recent neuropeptide, having appeared only with the emergence of mammals. Two peculiarly mammalian traits, uterine contraction and milk ejection, have long been associated with oxytocin release. In the brain, oxytocin seems to facilitate an entire range of affiliative behaviours [Insel, 1992; Winslow et al., 1993a], including parental behaviours [Insel and Shapiro, 1992a,b; Pedersen et al., 1992], reproductive behaviours [Argiolas et al., 1985; Cunningham and Sawchenko, 1991; Carter, 1992], and infant-mother attachment [Insel and Winslow, 1991; Pankseep, 1992].

The facilitatory role of oxytocin in affiliative behaviours may be mediated through an anxiolytic action. Oxytocin was found to be highly potent in reducing separation distress vocalizations in young chicks and rats, without producing any apparent sedation, even at high doses [Insel and Winslow, 1991; Pankseep, 1992]. Administration of an oxytocin receptor antagonist blocked this anti-separation anxiety effect, suggesting that the effect of oxytocin was specific [Insel and Winslow, 1991]. Centrally administered, oxytocin appeared to affect learning and memory processes [Argiolas and Gessa, 1991; Popik and Vetulani, 1991]. The amnestic effect of oxytocin may help females to forget the pain of labor and may also provide a general mechanism for anxiety reduction without sedation.

Oxytocin [Winslow et al., 1993a] and the chemically related neuropetide arginine-vasopressin [Winslow et al., 1993b] have been suggested to be involved both in behaviours associated with social dominance and formation of social bonds. Winslow and Insel [1991] have shown that oxytocin, administered centrally, increased the sexual and aggressive behaviour of dominant monkeys, without affecting the behaviour of subordinate ones.

Two closely related species of voles (*Microtus*) with dichotomous systems of social organization [Getz and Hofmann, 1986] show different patterns of oxytocin receptor distribution in the central nervous system (CNS) [Insel and Shapiro, 1992a,b]. Adult prairie voles (*Microtus ochrogaster*) form long-term, preferential relationships, are highly affiliative, and their pups frequently emit ultrasonic calls in response to social isolation. In contrast, Montane voles (*Microtus montanus*) are polygamous and minimally parental, and their young show minimal behavioural and endocrine responses to social isolation. Levels of oxytocin receptor expression correlate with this difference in behaviour between the two vole species; however, at parturition the montane voles exhibit maternal behavior and at that time, the level of expression of the oxytocin receptor is more similar to the pattern of expression ob-

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served in the prairie voles [Insel and Shapiro, 1992a,b]. Thus differences in the socializing effects of oxytocin could be exerted through altered function of this neurotransmitter's receptor.

The oxytocin receptor is a member of the GTP-binding protein seven transmembrane domain receptor family [Di Scala-Guenot and Strosser, 1992; Kimura et al., 1992]. The human cDNA encodes a 388 amino acid polypeptide with several possible sites for post-translational modifications [Kimura et al., 1992]. In rat brain [De Kloet et al., 1985; Van Leeuwen et al., 1985; Elands et al., 1988; Freund-Mercier et al., 1988a,b; reviewed in Tribollet et al., 1992] the oxytocin receptor is found in cells located on the posterior border of the anteroventral olfactory nucleus, the taenia tecta, the lateral segment of the bed nucleus of the stria terminalis, the dorsal-medial aspects of the caudate, the central nucleus of the amygdala, the ventral subiculum and in forebrain regions thought to be integrative centers. In addition, oxytocin receptors are found in brainstem autonomic nuclei, including the dorsal motor nucleus of the vagus and the nucleus of the solitary tract.

Recently, Yoshimura et al. [1993] showed that this pattern of receptor distribution was paralleled by the distribution of oxytocin receptor mRNA, as shown by in situ hybridization. Although no differences in the brain distribution of receptors were observed between male and female rats, the pattern of distribution was markedly different in the infant as compared to the adult [Tribollet et al., 1988a,b; 1991a,b].

Oxytocin receptor expression, both in the periphery and also in the CNS, is regulated by gonadal steroids [Insel, 1986; Johnson et al., 1989a,b, 1991; Shumacher et al., 1989, 1990; reviewed in McCarthy and Pfaff, 1993] and varies during pregnancy and the estrous cycle, both of which can alter the receptor expression in a regionally specific fashion [Insel, 1986; Jirikowsky et al., 1989].

Isolation of the cDNA for a human oxytocin receptor now allows a search for genetic variation at this gene to be conducted. In order to genetically map this gene and to provide a marker for linkage and association to oxytocin-related genotypes, we attempted to identify polymorphic alleles for the human oxytocin receptor. Within the previously published sequence of the 3′ nontranslated region of the human oxytocin cDNA is a stretch of 15 CA dinucleotide repeats (bases 2246–2277). Such stretches of CA repeats are often polymorphic, prompting us to evaluate this region for genetic variation. The CA repeat polymorphism we detected was used to genetically map the human oxytocin receptor.

PCR was used to amplify a 274 bp fragment of the 3′ untranslated region of the oxytocin receptor gene. This region contained a 30 bp CA stretch bp 2246–2277 in the published cDNA sequence [Kimura et al., 1992]. The sense and antisense primers were $^{5'}$AAAAGAAATAAATGTATCCA$^{3'}$ and $^{5'}$TTGATTCCTATTTTATTCTT$^{3'}$, respectively. The sense primer was synthesized with an Aminolink-2 (Applied Biosystems, Foster, CA) residue incorporated at the 5′ terminus and was labeled with the blue (Fam) fluorescent phosphoramidite dye (Applied Biosystems) subsequent to synthesis. The labeling was carried out according to the manufacturer's recommendation [Ziegle et al., 1992; Giusti and Adriano, 1993]. After labeling, primers were purified from unincorporated dye using G-25 Sephadex columns. Labeled primers were purified from unlabeled primers using oligonucleotide purification columns (Applied Biosystems).

For PCR, 50 ng of total genomic DNA was amplified in the presence of 0.2 μM of each primer, 200 μM of each dNTP, 10 mM Tris-HCl (pH 8.3 at 25°C), 50 mM KCl, 1.5 mM Mg Cl_2, 0.001% (w/v) gelatin, and 0.4 units of Taq polymerase (Perkin-Elmer Cetus, Norfolk, CT) in a total volume of 10 μl. After a 2 min denaturation at 95°C samples were amplified for 30 cycles by denaturing for 15 sec at 95°C, annealing for 15 sec at 45°C and extending for 30 sec at 72°C in a 9600 thermocycler (Perkin-Elmer Cetus, Norfolk, CT). After the last cycle an additional 5 min extension at 72°C was carried out.

For electrophoresis of amplified DNA fragments, a mixture containing 3 μl of PCR products, 5 μl of formamide, and 0.5 μl of internal size standards was prepared and incubated at 100°C for 5 min. The internal size standards were GeneScan 2500 ROX (Applied Biosystems), which is a PstI digest of lambda phage labeled with red dye (ROX) by a ligation method [Carrano et al., 1989]. Seven microliters of this denatured DNA was loaded per lane and electrophoresed on a denaturing 5% polyacrylamide 6M urea gel using a 373A DNA Sequencer (Applied Biosystems, Foster, CA). The gel results were analyzed using Genescan 672 software (Applied Biosystems).

Human/mouse and human/hamster monochromosomic hybrid cell lines (Camden Mutant Cell Repository) were evaluated by PCR. In addition, the parents of all of the Centre du Etude du Polymorphisme Humain (CEPH) families were genotyped as well as the informative families. Data were entered into the programs provided by CEPH, and, based on the results from the chromosomal assignment, files with chromosome 3 markers were prepared. Two-point linkage analyses were performed using MAPMAKER [Lander et al., 1987], and the two-point values were also utilized in a multipoint analysis. Multipoint linkage analysis was performed using linked markers from both the Genethon [Weissenbach et al., 1992] and NIH/CEPH consortium [1992] maps. A map of markers of known order from 3p was assembled, and the human oxytocin receptor gene was located on the map by the TRY function of MAPMAKER. All primary data have been contributed to CEPH and are freely available [Dausset et al., 1990].

To provide a genetic marker for linkage and association studies of traits influenced by oxytocin receptor functions, we screened for polymorphism a region of the 3′ nontranslated region which contains a 30 bp repeat sequence. Such short tandem repeat (STR) regions have been shown often to be highly polymorphic [Weber and May, 1989; Tautz, 1989; Smeets et al., 1989; Litt and Luty, 1989]. Genomic DNAs from 70 unrelated Caucasian CEPH parents were evaluated. Two alleles were detected, the fragment differing in size by two base pairs (Fig. 1). In the Caucasians the frequency of the smaller allele (allele A) is 0.77.

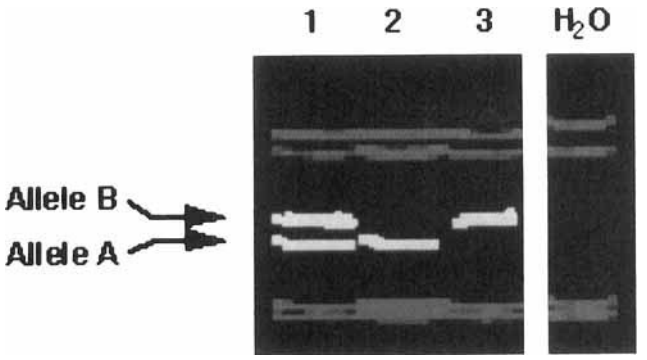

Fig. 1. STR analysis of oxytocin receptor gene polymorphism. Genomic DNA was amplified as described in Material and Methods from individuals heterozygous for the A and B alleles **(lane 1),** homozygous for the A allele **(lane 2),** and homozygous for the B allele **(lane 3)** of the human oxytocin receptor gene. PCR samples were electrophoresed under denaturing conditions on an 5% acrylamide 6M urea gel in an ABI 373 DNA Sequencer.

The polymorphism was used to genetically map the oxytocin receptor gene. Human/mouse and human/hamster hybrid cell lines were analysed for the presence of the human oxytocin receptor gene using fluorescent PCR as described above. Human genomic DNA and all hybrid cell lines containing human chromosome 3 showed a positive signal for the human oxytocin receptor gene, as seen in Figure 2. Neither mouse nor hamster control DNAs gave an amplification signal. These results localized the human oxytocin receptor gene on chromosome 3.

Genetic mapping of the human oxytocin receptor gene was carried out against markers previously mapped to chromosome 3, and using eight CEPH families in which the parents had genotypes informative for linkage. Significant linkage results are shown in Table I. Human oxytocin receptor showed zero recombinants and a Lod score of 4.82 with D3S726, which had been previously localized to 3p26 [Tory et al., 1992]. Multipoint linkage analysis placed human oxytocin receptor between D3S1304 and D3S1263 (data not shown).

In this study, we report a CA repeat polymorphism within the 3′ nontranslated region of the human oxytocin receptor cDNA. The two alleles detected in Caucasians differ in size by two base pairs and have frequencies of 0.77 and 0.23. The detected polymorphism allowed us to genetically map the human oxytocin receptor gene on chromosome 3p25-3p26, in a region which contains loci for several important genes, including the gene for von Hippel-Lindau disease (VHL) [Latif et al., 1993]. VHL is a rare autosomal dominant disease exhibiting variable penetrance and expressivity in predisposing to the development of haemangioblastomas of the central nervous system and retina, renal cell carcinoma and phaeochromocytoma. VHL is thought to be caused by loss of function of a tumor suppressor gene [Latif et al., 1993]. The interval RAF1-D3S18 (3p25-3p26) has been identified by linkage studies to harbour the VHL gene [Richards et al., 1993].

To this point, no genetically influenced human behavioural difference or psychiatric disease has been mapped to the 3p25-3p26 region. As alluded to in the Introduction, an oxytocin receptor mutation could alter a variety of reproductive and social behaviours [reviewed in Insel, 1992]. After gonadal steroid priming, oxytocin promotes sexual readiness and is an important stimulus for ejaculation. During parturition, it induces uterine contraction. After delivery, oxytocin release is stimulated by suckling and in turn facilitates milk ejection.

In animals, oxytocin has also been shown to be involved in the infant-mother attachment and to influence behaviours associated with social dominance and formation of social bonds. However, the extent to which oxytocin is involved in any aspect of affiliation and social bonding in humans remains entirely speculative.

Recently Pankseep [1992] suggested that an oxytocin-mediated deficit in social bonding could cause the

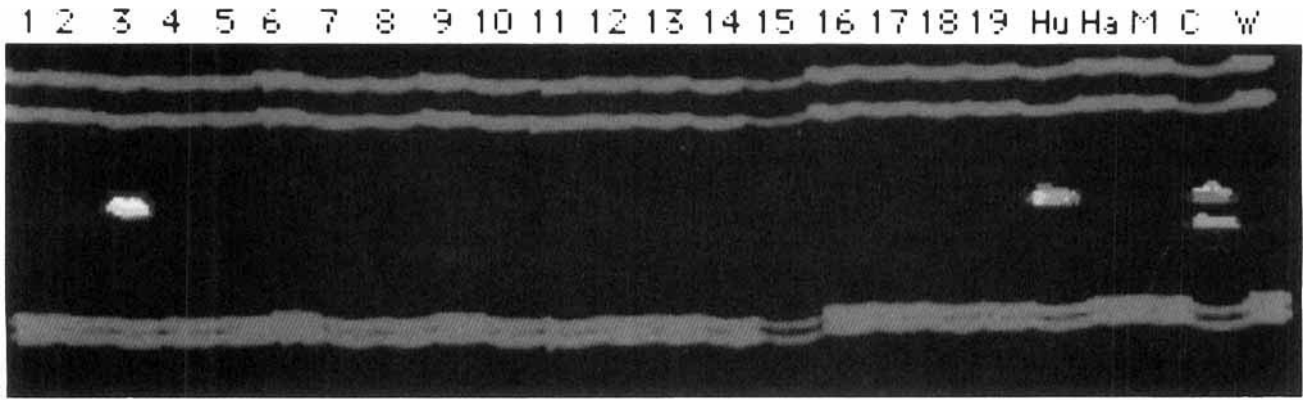

Fig. 2. Chromosomal localization of the human oxytocin receptor gene. Human/mouse and human/hamster hybrid cell lines were analysed for the presence or absence of the human OR gene using fluorescent PCR. Samples run in each lane are identified above the lane. Each cell hybrid the cell line is identified by the human chromosome which is retained. The control lanes include genomic DNA from the original cell lines which were used to generate the cell hybrids human (Hu), hamster (Ha), mouse (M) cell lines, as well as a human genomic DNA positive control (C) and a water negative control (W).

TABLE I. Markers Linked to the Human Oxytocin Receptor Gene*

Locus	Probe	Enzyme	Location	θ	Z_{max}
D3S198	23–58	Taq I	3p	0.00	3.91
D3S238	48–95c	Taq I	3p	0.10	5.67
D3S726	4A–54d	Msp I	3p26	0.00	10.23
D3S1263	079yg5	ACn	3	0.10	8.05
D3S1279	217xd2	ACn	3	0.11	5.50
D3S1259	036yb8	ACwn	3	0.14	3.54
D3S1286	197xg11	ACn	3	0.12	5.25
D3S1304	234tf4	ACn	3	0.15	4.38
D3S1597	295yc9	ACn	3	0.03	6.51

* The D3S markers are anonymous loci. "Enzyme" refers to the enzyme that detects the polymorphism. "Location" is the known physical location of the marker on chromosome 3. "θ" is the sex-averaged recombination frequency observed with the human oxytocin receptor gene and "Z_{max}" is the LOD (log of the odds) score at that value of the recombination frequency.

social reticence of autistic children and schizophrenics and the social avoidance of certain social phobic patients. An impairment in central oxytocinergic transmission could also be involved in separation anxiety disorder, panic disorder and antisocial personality disorder.

In the human, anxiety is a highly heritable trait and there is a cluster of anxiety-related psychiatric disorders for which the oxytocin receptor could be one candidate gene. In childhood, separation anxiety results due to removal from an environment, object, or person to which an attachment has been formed. Some children resist or refuse many forms of normal separation, such as sleeping alone, venturing out alone for play or attending school. Individuals with separation anxiety disorder have been reported to have first-degree relatives both with separation anxiety [Gittelman Klein, 1975; Weissman et al., 1984] and also with panic disorder [Weissman et al., 1984], which is itself a highly heritable condition [reviewed in Torgersen, 1990].

Detection of a human oxytocin receptor polymorphism will enable genetic linkage and population studies to be performed in these psychiatric disorders. For these studies, either the oxytocin receptor CA repeat described here or closely linked and more highly informative markers can be used.

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