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Brief Research Communication

Oxytocin and Vasopressin as Candidate Genes for Psychiatric Disorders: Lessons From Animal Models

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Multiple approaches should be taken to investigate the genetic bases of psychiatric disorders, including the consideration of candidate genes. Studies in animal models suggest that the genes encoding oxytocin, vasopressin, and their respective receptors should be considered in a candidate gene approach for psychiatric disorders involving social deficits, such as autism or social phobias. These neuropeptide hormones may mediate the rewarding nature of social interactions and have been implicated in social attachment and social recognition in several animal models. Mutations in genes unrelated to oxytocin and vasopressin have been shown to have secondary effects on neuropeptide function and subsequent behavioral phenotypes. Genetic analysis of polymorphisms and expression analysis of candidate genes implicated in animal models may prove useful for determining the molecular mechanisms underlying psychiatric disorders, particularly in cases where other techniques proven difficult. Am. J. Med. Genet. (Neuropsychiatr. Genet.) 105: 53–54, 2001. © 2001 Wiley-Liss, Inc.

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Genetic analyses utilizing sibling or twin studies and genome scans are powerful mechanisms for identifying genes involved in psychiatric disorders. Many of the genes identified with these techniques have unknown functions, making it difficult to establish a conceptual link between the genetic defect and the phenotypes associated with the disorder. In addition, many traits are clearly multigenic in nature, or sufficiently rare to make the identification of causal genetic relationships difficult. In such cases identification of candidate genes may be particularly useful. Data from animal research can be useful for identifying candidate genes. As an example, the neuropeptide hormones oxytocin and vasopressin and their respective receptors are excellent candidate genes for exploration in certain psychiatric disorders, particularly those involving social impairments.

Oxytocin and vasopressin are synthesized in the hypothalamus and receptors for these hormones are located in brain regions associated with social behavior and emotionality. Research in a wide range of mammalian species indicate that oxytocin plays an important role in various types of prosocial behaviors. Oxytocin facilitates the formation of the mother–infant bond in sheep [Kendrick et al., 1997] and stimulates nurturing behaviors in rodent females toward pups [Pedersen et al., 1994]. Within minutes after delivery ewes form a selective bond with their lamb and subsequently provide parental care to that lamb. Oxytocin is released within the brain at the time of delivery. If oxytocin transmission is prevented, the ewe fails to form the selective bond with her lamb. Infusing oxytocin into the brain of a nonpregnant ewe will stimulate her to bond with an unfamiliar lamb. In humans, oxytocin plays a role in stimulating or maintaining labor and is responsible for the milk ejection reflex during nursing. Mothers who deliver by cesarean section have fewer oxytocin pulses during breastfeeding than those who give birth vaginally. In mothers delivering by cesarean section, oxytocin levels are correlated with the degree of openness to social interactions and with calmness [Nissen et al., 1998].

In male rats, chronic oxytocin treatment doubles the time spent in social contact [Witt et al., 1992]. Oxytocin is also essential for social recognition in mice. Oxytocin knockout mice fail to behave as if they recognize individuals to which they have been repeatedly exposed [Ferguson et al., 2000]. This condition can be corrected by a single injection of oxytocin into the brain prior to the initial encounter. Juvenile social behavior is also influenced by oxytocin. When rat pups are isolated from their mothers, they emit ultrasonic calls in protest. Oxytocin can calm those calls and oxytocin knockout mice produce significantly fewer protest calls, as if isolation is not distressful to them [Ferguson et al., 2000; Winslow et al., 2000]. These and other observations have led to the hypothesis that oxytocin mediates many of the positive, rewarding qualities of social contact.

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Vasopressin, which is structurally very similar to oxytocin, also modulates social behaviors. Vasopressin stimulates social communication in birds, frogs, and hamsters, stimulates aggression in hamsters, and increases affiliative and paternal behaviors in voles [Young, 1999; Young et al., 1999]. In many species, vasopressin is sexually dimorphic, with males having higher levels within the brain than females [De Vries, 1990].

Voles have been particularly useful models for examining the roles of oxytocin and vasopressin in modulating social behaviors [Young et al., 1998]. Prairie voles are highly social, are monogamous, and exhibit biparental care. After mating, prairie vole pairs form lifelong social attachments, or pair bonds. They live in communal burrows occupied by multiple generations of offspring. In contrast, montane voles do not form social attachments between mates and prefer to spend time alone rather than in groups. Female montane voles nest alone and abandon their pups after just 2 weeks of care. Oxytocin facilitates the bonding of the female to the male following mating. For example, a female prairie vole will bond with a male, even in the absence of mating, if she is injected with oxytocin prior to their encounter. Blocking oxytocin receptors with specific antagonists prevents the formation of a bond, even with extended mating bouts. Likewise, vasopressin stimulates, and vasopressin receptor antagonists block, the formation of a bond between the male with his female partner. What explains the differences in behavior between the two vole species? Montane and prairie voles have similar levels of oxytocin and vasopressin in the brain, but the distribution of the receptors for these hormones in the brain differs dramatically between the two species. These differences in receptor distribution are probably linked to the differences in behavior since transgenic mice with a prairie vole pattern of receptor expression display increased affiliative behavior when injected with vasopressin, a response not seen in normal mice [Young et al., 1999]. Significant differences in the vasopressin receptor promoter sequence accompany the differences in receptor gene expression in the brain. The differences are concentrated in a large stretch of repetitive dinucleotide and tetranucleotide repeats just upstream of the transcription start site of the prairie vole receptor gene [Young et al., 1999]. The human vasopressin receptor gene has similar repetitive elements in this region, and we have detected polymorphisms in the numbers of these repeats, which may prove useful in linkage analysis studies. This data suggests that genetic changes in noncoding regions of receptor genes may influence the tissue-specific specific pattern of gene expression, which may impact the expression of social behaviors.

Given the important social roles of these hormones, the oxytocin and vasopressin systems are excellent targets in a candidate gene approach involving disorders with social impairments. For example, autism spectrum disorders are associated with social impairment, including lack of social reciprocity and failure to recognize the uniqueness of others, communication abnormalities, and stereotyped behavior. This disorder has a higher prevalence in males compared to females. One study has found that plasma oxytocin levels in autistic children were approximately one-half the levels found in controls [Modahl et al., 1998]. To date, no genetic studies have found a link between oxytocin or vasopressin, which are linked and map to 20p12.2, and any psychiatric disorder. Family and twin studies have demonstrated a genetic component to autism, but suggest oligogenetic inheritance. Disruptions in a number of genes could impact social behavior through pleiotropic effects on the oxytocin or vasopressin systems. For example, a recent study discovered a disruption in nurturing behavior in mice in which the *peg3* gene had been deleted [Li et al., 1999]. The *peg3* gene is a developmental gene with unknown function. The homozygous knockout mice had dramatically decreased numbers of oxytocin-producing neurons in the hypothalamus, providing an explanation for the disrupted maternal care.

In summary, animal studies suggest that oxytocin and vasopressin should be considered in candidate gene approaches for disorders involving social deficits. Furthermore, defects in other genes could be modulating these neuropeptide systems, which then contribute to the complex phenotype. Gene expression analysis studies, such as DNA microarrays, may provide another useful tool in examining the pleiotropic effects of genetic mutations on the expression of a host of candidate genes. This approach may be useful in determining the link between genetic mutations and the disruption of specific hormonal and neurotransmitter systems, which can then be targeted for pharmacological intervention.

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