A Neurobiological Basis of Social Attachment

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Objective: *Although an inability to form normal social attachments characterizes many forms of psychopathology, there has been little study of the neural basis of social bond formation. The primary purpose of this article is to describe a novel approach to the neurobiology of attachment.* *Method:* *The author reviews animal research on two closely related neuropeptides, oxytocin and vasopressin, implicated in the central mediation of attachment behaviors. These neuropeptides appear to be important for the initiation of pair bonds and parental behaviors as well as the infant's response to social separation.* *Results:* *Both cellular and molecular studies have begun to reveal the mechanisms by which oxytocin and vasopressin neural pathways are regulated, leading to a preliminary understanding of how these hormones act within the brain to influence complex social behaviors.* *Conclusions:* *Although their function in the human brain has yet to be demonstrated, the available evidence suggests that oxytocin and vasopressin may prove to be important in the pathophysiology of clinical disorders, such as autism, characterized by an inability to form normal social attachments.*

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Since Bowlby's seminal contributions (1), attachment and separation have become familiar theoretical components of ego psychology, developmental psychology, and psychodynamic theory. In spite of the important roles these concepts have played in studies of psychological development, relatively little is known about their neurobiological basis. If one considers that abnormal social attachments characterize virtually every form of psychopathology, it seems especially remarkable that the chemistry, the anatomy, and the physiology of social bond formation remain largely unexplored. To be sure, there is a considerable literature on the neurobiology and psychobiology of separation (2), but this work may not prove instructive for understanding social bond formation. Attachment is not simply the absence of separation. Accordingly, there is no obvious reason why attachment and separation should be subserved by the same neural pathways.

Attachment, of course, is not a thing but a process (3). More specifically, it is a social process and thus not likely to be defined by a single neurochemical pathway nucleus or represented in a single anatomic nucleus. As Harlow noted throughout his insightful writings on this subject (4), attachment includes several quite different processes depending on the social context: parent-infant, filial, and pair (male-female) bond formation are all forms of attachment. All of these forms involve seeking proximity and all involve a response to separation, but the strategy for and the consequences of achieving proximity vary depending on the relationship. None of these forms of attachment is uniquely human, suggesting that the neural basis can be investigated in animal models. It is also possible (and experimentally testable) that these various forms of attachment use similar neural pathways, suggesting that, biologically, attachment is a singular process that is manifested with different behaviors depending on the external (e.g., social) or internal (e.g., endocrine) context.

This review will describe research on two neuropeptides, oxytocin and vasopressin, that have been implicated in the central mediation of attachment. I will de-

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scribe these neuropeptides and then review the evidence from studies in laboratory animals implicating these peptides in each of the forms of attachment behavior. Finally, I will suggest the implications of this work for studies of abnormal social behavior in our own species.

NEUROHYPOPHYSEAL NEUROPEPTIDES

Oxytocin and vasopressin, nine-amino-acid peptides (nonapeptides) synthesized in the hypothalamus, are released into the bloodstream through axon terminals in the posterior pituitary or neurohypophysis (hence their designation as neurohypophyseal peptides). The peptides are closely related structurally, differing in only two amino acids (figure 1). Both are part of a family of nonapeptides that can be traced phylogenetically to invertebrates (5). Ancestral nonapeptides have been implicated in various forms of nonmammalian reproductive behaviors such as nest building. Oxytocin and vasopressin are unique among this family in that they are found exclusively in mammals, probably evolving from the ancestral peptide arginine vasotocin, from which oxytocin and vasopressin each differs in only a single amino acid (figure 1) (6).

It may be no coincidence that these peptides have been implicated in prototypically mammalian functions. Oxytocin, for instance, has an important role in milk ejection during nursing and uterine contraction during labor. The traditional view of the neurohypophyseal peptides as endocrine hormones acting on peripheral organs has been revised to consider these peptides as neurotransmitters or neuromodulators, that is, peptides with central actions. Not only do hypothalamic cells synthesizing oxytocin or vasopressin project to diverse sites within the brain and brainstem (7), but receptors for both peptides have been found throughout the limbic system in the forebrain and autonomic centers in the brainstem (8). Furthermore, both peptides are released within the brain following chemical depolarization of the appropriate neurons, and fibers have been demonstrated at the ultrastructural level to make synaptic contacts in the central nervous system (CNS) (9). Thus, the evidence is quite strong that the brain is a target organ for these peptides.

We now have almost 3 decades of research indicating that both peptides have important central effects (10, 11). The preponderance of this literature has focused on their roles in the modulation of memory, the regulation of fluid balance, and the response to hyperthermia. A growing body of evidence (12–14) implicates oxytocin and vasopressin in the central mediation of complex social behaviors.

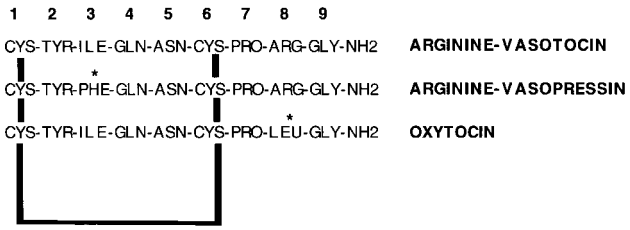
PAIR BOND FORMATION

The development of adult-adult pair bonds is certainly the least studied form of attachment from a neurobiological perspective. The relative paucity of studies can be attributed to the absence of pair bonds in commonly used laboratory animals, such as rats and mice. By definition, pair bonds occur in monogamous animals, and approximately 3% of mammals currently are considered monogamous (15, 16). The percentage of primates that are monogamous is considerably higher (perhaps 15%) (17). Studies in nonhuman primates have provided important insights into both behavioral and endocrine aspects of monogamy (18, 19), but research on the neurobiological basis of pair bonding will ultimately require investigations of monogamous nonprimate species that can be used for cellular and molecular studies.

The prairie vole (*Microtus ochrogaster*) is a mouse-sized rodent that lives in burrows across the American Midwest. Prairie voles are usually found in multigenerational family groups with a single breeding pair (20, 21). They manifest the classic features of monogamy: a breeding pair shares the same nest and territory where they are in frequent contact, males participate in parental care, and intruders of either sex are rejected. Following the death of one of the pair, a new mate is accepted only about 20% of the time (the rate is approximately the same whether the male or the female is the survivor) (22). Prairie voles also demonstrate a curious pattern of reproductive development. Offspring remain sexually suppressed as long as they remain within the natal group. For females, puberty occurs not at a specific age but after exposure to a chemosignal in the urine of an unrelated male (23). Within 24 hours of exposure to this signal, the female becomes sexually receptive. She mates repeatedly with an unrelated male and, in the process, forms a selective and enduring preference or pair bond (24).

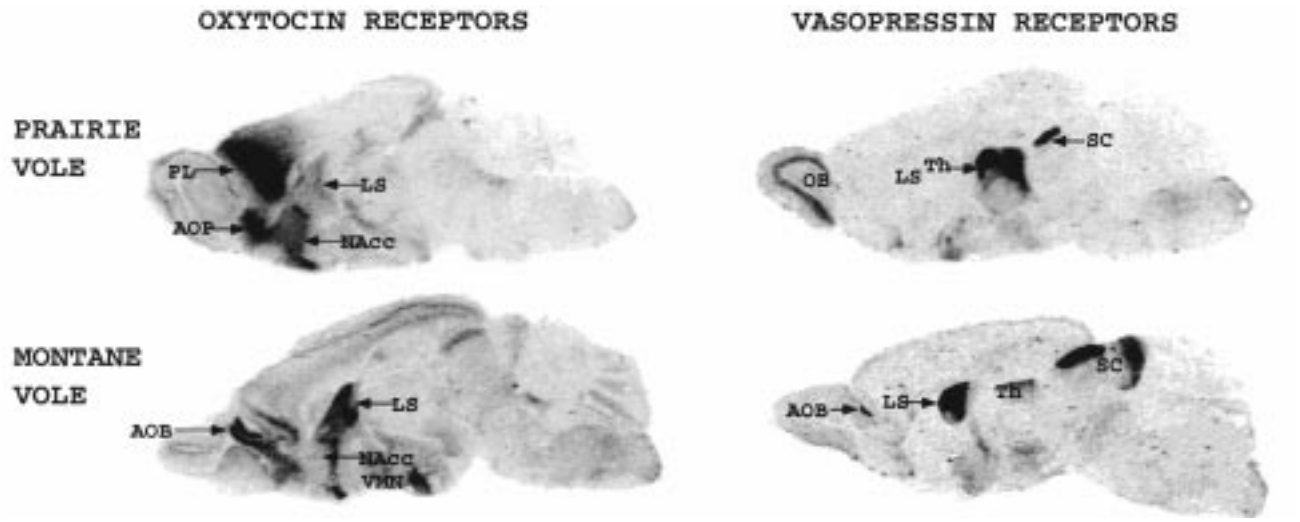
Two aspects of the prairie vole make this species particularly useful for neurobiological investigation. The first is that the highly developed social behaviors described in field studies are also manifest in the laboratory with either captive or laboratory-bred animals. In the laboratory, prairie voles appear highly affiliative, sitting side by side more than 50% of the time and attacking adult intruders (24, 25). Both sexes display in-

FIGURE 1. Nine-Amino-Acid Structure of Arginine-Vasotocin, Arginine-Vasopressin, and Oxytocin[a]



[a]Arginine-vasotocin is an ancient peptide, implicated in reproductive behaviors in reptiles, amphibians, and birds. Vasopressin and oxytocin have evolved with mammals, through a single amino acid change at either the second position (vasopressin) or the eighth position (oxytocin). The asterisks indicate sequence differences.

FIGURE 2. Autoradiograms of Oxytocin and Vasopressin Receptor Binding in Prairie Voles and Montane Voles[a]



[a]Images from sagittal sections show dark areas where receptors bind [^{125}I]oxytocin A, a selective oxytocin antagonist, or [^{125}I]sarc-vasopressin, a selective vasopressin antagonist. For oxytocin receptors, differences between vole species are apparent in the prelimbic region (PL), lateral septum (LS), anterior olfactory nucleus (AOP), accessory olfactory bulb (AOB), nucleus accumbens (Nacc), and thalamus (Th). For vasopressin receptors, species differences are apparent in the main olfactory bulb (OB), lateral septum (LS), and thalamus (Th) but not in the superior colliculus (SC). More detailed receptor maps for these and other vole species can be found elsewhere (32, 33).

tense parental care (26, 27). Even neonatal prairie voles appear to crave social contact. During a brief social separation, 5-day-old prairie voles emit ultrasonic "distress" calls and secrete corticosterone (28).

As a second virtue for research, prairie voles offer the possibility of comparative studies. The closely related montane vole (*Microtus montanus*) looks remarkably similar to the prairie vole and shares many features of its nonsocial behaviors but differs consistently on measures of social behavior (16, 29). Montane voles are generally found in isolated burrows (in high meadows in the Rockies), show little interest in social contact, and are clearly not monogamous (30). Males show little if any parental care and females frequently abandon their young between 8 and 14 days postpartum (31). In laboratory studies, montane voles spend little time in side-by-side contact, even within the confines of a mouse cage (25). Montane pups at day 5 do not respond to social separation with either isolation calls or corticosterone release, although the pups give both responses to nonsocial stressors (28).

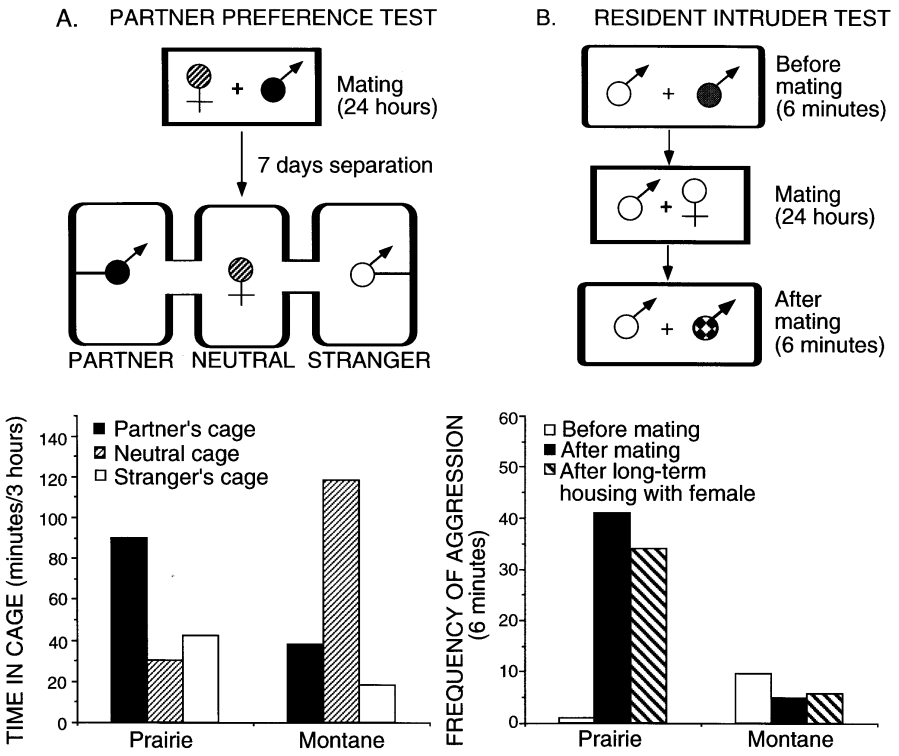
Prairie and montane voles thus provide an intriguing natural experiment for studying the neural substrates of pair bonding. Do these species differ with respect to central pathways for oxytocin or vasopressin? In fact, the species differ in the neural distribution of receptors for both peptides as much as they differ in behavior (32, 33). These receptors show similar binding characteristics (in terms of kinetics and specificity) in the two species, but the receptors are expressed within entirely different pathways (figure 2). This difference between species in regional receptor distribution indicates that different brain areas are responding to these peptides and, therefore, that the central effects of oxytocin and vasopressin should be quite different in prairie and montane voles. For instance, in the prairie vole, oxytocin receptors are found in brain regions associated with reward (the nucleus accumbens and prelimbic cortex), suggesting that oxytocin might have reinforcing properties selectively in this species. Conversely, receptors in the lateral septum, found only in the montane vole, might be responsible for the effects of oxytocin or vasopressin on self-grooming, an effect that is observed in the montane vole but not the prairie vole.

Three observations suggest that the differences in receptor distribution may be related to the differences between the species in social behavior. First, other vole species (pine voles and meadow voles) selected for analogous differences in social organization (i.e., monogamous versus nonmonogamous) manifest similar differences in receptor distribution for both oxytocin and vasopressin (32, 33). Second, the findings with oxytocin and vasopressin receptors appear relatively specific: the patterns of binding for μ opiate receptors and benzodiazepine receptors (two systems previously implicated in the mediation of social attachment) do not differ across the four vole species (32). Finally, after parturition, when the female montane vole becomes briefly parental, the pattern of oxytocin receptor binding changes to resemble the pattern observed in the highly parental prairie vole (32).

Although these anatomic data are consistent with a role for either oxytocin or vasopressin in the behavioral differences observed in prairie and montane voles, these descriptive experiments fail to address the central question: is either peptide involved in pair bonding? To address the role of these peptides directly, two operational measures of pair bonding have been applied (figure 3) (34, 35). The first measure examined partner preference

with a choice test. It was assumed that formation of a pair bond requires the formation of a preference for the mate over a stranger. Indeed, in tests of this assumption, prairie vole females reliably chose to sit next to their mates, but female montane voles were equally likely to sit with a novel male as with the male with whom they had mated (figure 3). This partner preference is enduring and reciprocal. Prairie voles continue to show a preference for their mates even after weeks of separation, and this preference can be detected in both males and females (34, 36). A second test of bonding was derived from the observation that male prairie voles become highly aggressive after mating. This aggression is selectively directed at intruders and appears to serve the function of mate guarding (36). Curiously, the aggression persists for at least a week, even in the absence of the mate, and continues to be expressed toward both adult males and females for several months if the mate remains present (35). Montane voles do not show this induction of aggression after mating, further supporting the validity of this measure as an indicator of pair bonding (35).

FIGURE 3. Operational Definitions of Pair Bonding in Prairie Voles and Montane Voles[a]

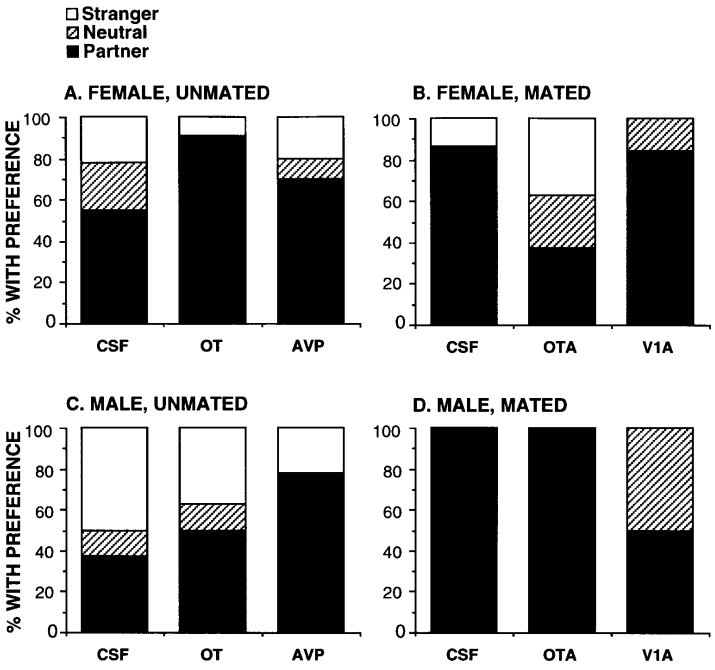


[a]Behavioral measures of pair bonding include the partner preference test (A) and the resident intruder test (B). In the partner preference test, a female is placed with a male for 24 hours, then tested for preference for the original male (partner) or a novel male (stranger). Males are tethered in their respective cages, while the female, initially placed in a central cage (neutral cage) has free access to all three cages. In a 3-hour preference test, prairie voles (N=10) spent more time in the partner's cage, but the montane voles (N=9) spent more time in the neutral cage. In the data shown (from reference 34), females were separated from their mates for 7 days before partner preference testing. No species differences were apparent in mating behavior, and significant differences between species in the amount of time spent with the mate were evident immediately after mating. In the resident intruder test, for a pretest, an intruder is placed for 6 minutes in the male's home cage. Following 24 hours of mating, the experimental male receives a second intruder test with a new male. In the highly affiliative prairie vole (N=9), the frequency of aggression was minimal before mating but increased almost 40-fold within 24 hours; this increase was sustained for several months, as shown by testing after long-term housing with females (breeders). In the montane voles (N=7), mating had no apparent effect on intruder aggression. Data adapted from Winslow et al. (35).

If mating facilitates pair bond formation and oxytocin is released with mating, does oxytocin influence the development of the pair bond? As shown in figure 4, oxytocin (but not vasopressin) given centrally to female prairie voles facilitates the development of a partner preference in the absence of mating (34, 37). A selective oxytocin antagonist given centrally before mating blocks formation of the partner preference without interfering with mating (34). This effect appears specific: neither CSF nor a vasopressin antagonist given in an identical fashion blocks formation of the partner preference. Presumably, the oxytocin antagonist prevents the binding of oxytocin to its receptor and thereby blocks the behavioral consequences of mating. These results suggest that oxytocin released with mating is both necessary and sufficient for the formation of a pair bond in the female prairie vole. Essentially, female prairie voles given the oxytocin antagonist resemble montane voles—they mate normally but show no lasting interest in their mate.

What about the male in this process? Males show a partner preference and increased aggression after mating, but it is not oxytocin but vasopressin that is critical. As shown in figure 4, a vasopressin antagonist administered centrally to male prairie voles before mating blocks the development of both the partner preference and the selective aggression (35). As with females, the antagonist does not interfere with mating; rather, it appears to block the consequences of mating. Moreover, the antagonist is not antiaggressive per se. Males treated after mating show no reduction of attack behavior (35). An oxytocin antagonist has no effects on these behaviors, suggesting that the vasopressin effects are specific. Vasopressin may also be sufficient for male pair bonding. When males are not permitted to mate but are exposed to ovariectomized females, they show

FIGURE 4. Effects of Oxytocin and Vasopressin on Partner Preference in Male and Female Prairie Voles[a]



[a]Partner preference tests were used to determine if oxytocin (OT) or vasopressin (AVP) is necessary or sufficient for pair bond formation in a monogamous mammal. Peptides, selective antagonists (oxytocin receptor antagonist [OTA] and vasopressin 1A receptor antagonist [V1A]), or CSF were administered into the lateral ventricle during social exposure. Following social exposure, the percentage of a 3-hour test spent in the partner's, stranger's, or neutral cage (figure 3) was measured. In A, if females were placed with a male but did not mate, a partner preference was not observed unless oxytocin (0.5 ng/hour) was administered centrally during social exposure (N=11). Females given an equal dose of vasopressin (N=10) were not different from those treated with CSF (N=9). In B, females allowed to mate for 14 hours developed a partner preference (as expected from the partner preference test in figure 3) with central injection of CSF (N=6). Females given a vasopressin antagonist (5.0 ng) also showed a significant partner preference (N=8). Females given an oxytocin antagonist (5.0 ng) mated normally but failed to form a partner preference (N=7). Taken together, A and B suggest that oxytocin (released with mating) is sufficient and necessary for formation of a partner preference in female prairie voles. The males showed an opposite pattern. In C, neither CSF (N=8) nor oxytocin (0.5 ng/hour, N=8) supported formation of a partner preference in unmated males, but vasopressin (0.5 ng/hour, N=9) appeared sufficient. In D, when males had the opportunity to mate, the vasopressin antagonist (5.0 ng, N=6), but not CSF (N=6), or the oxytocin antagonist (5.0 ng, N=7), blocked partner preference formation. Thus, in contrast to females, vasopressin appears necessary and sufficient for formation of a partner preference in male prairie voles. Data adapted from Insel et al. (34, 36).

neither the partner preference nor the selective aggression. However, when vasopressin is given centrally, in the absence of mating, males show both measures of bonding—the partner preference and the aggression (35). Oxytocin given in the same fashion has no effect on these measures.

In summary, monogamous voles show different patterns of oxytocin and vasopressin receptor distribution in the brain, and both peptides appear to be important for pair bond formation, a process that occurs in monogamous animals. Recent data on the molecular structure of oxytocin and vasopressin receptors have provided a model for the evolution of monogamy (38). It is remarkable that the two peptide systems have been adapted for different roles in male and female prairie voles. Apparently, pair bonding in male and female voles activates two different, albeit closely related, neural systems.

Humans form enduring, selective bonds, but the role of central oxytocin or vasopressin in this process remains largely unexplored. Across human cultures, sexual behavior is consistently associated with pair bonding, although sex is neither necessary nor sufficient for human pair bond formation (39). Both neurohypophyseal peptides are released into plasma during human sexual behavior: in males, vasopressin peaks during arousal, and oxytocin peaks with ejaculation (40). One might speculate that the coordinated release of these neuropeptides into specific neural pathways during sexual intercourse facilitates the formation of a pair bond, as shown in prairie voles. Of course, to influence pair bond formation in humans, the receptors for these peptides would need to be located in sites homologous to those found in monogamous species. Receptors for both neuropeptides are found in the human brain, although the patterns of distribution do not resemble the patterns of either the monogamous prairie vole or the promiscuous montane vole (41). Oxytocin receptors are concentrated in the basal forebrain cholinergic nuclei, the nucleus basalis of Meynert, and the diagonal band of Broca (consistent with a role in memory). In addition, receptors are found in the preoptic area of the hypothalamus, an area considered important for the mediation of reproductive behaviors. Vasopressin receptors are concentrated in the lateral septum and the amygdala of the human brain, limbic areas with rich interactions with the hippocampus and anterior hypothalamus. Although there are neither pharmacological nor physiological data from humans with which to support or disprove a role for central oxytocin or vasopressin in pair bonding, studies in nonhuman primates demonstrate that increased neurotransmission of either oxytocin or vasopressin influences social interaction (42).

PARENTAL BEHAVIOR

In the same way that the prairie vole has proven useful for the study of pair bonding, the laboratory rat has been an ideal subject for studies of maternal care (43). Unlike many mammals, female rats show little interest in infants of their own species until just before parturition. About

a day before delivery, they shift from avoiding pups to showing intense interest, with avid nest building, retrieval, grooming, and defense of the young. These behaviors persist through lactation, then abate with weaning. Rats, therefore, provide an opportunity to study two quite distinct aspects of maternal care: its onset and maintenance. For studies of attachment, the onset—the transition from avoidance to intense interest—is of particular importance.

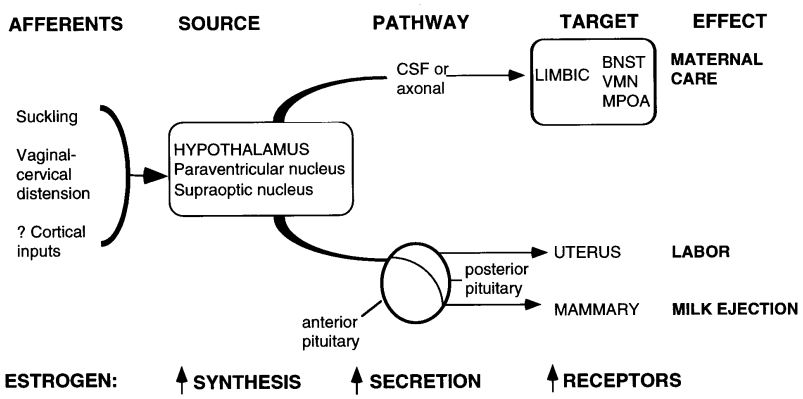
Several investigators have reported that oxytocin given centrally to estrogen-primed, nulliparous female rats facilitates the onset of maternal behavior. In the first such report, Pedersen and Prange (44) noted that the effect was specific to oxytocin (the only other neuropeptide with significant, albeit weaker, effects was vasopressin) and rapid (onset within 30 minutes). Perhaps even more remarkable, blockade of oxytocin neurotransmission by means of central injection of an antagonist or antiserum or by lesions of oxytocin-producing cells in the hypothalamus results in a significant inhibition of maternal behavior (reviewed in reference 12). These various interventions appear to inhibit the onset but not the maintenance of maternal behavior—an oxytocin antagonist or a lesion has no effect on maternal care once a female begins to show interest in pups (12). These results support the notion that oxytocin is necessary for the transition to maternal attachment to pups and that a central increase in oxytocin given under the appropriate gonadal steroid conditions might facilitate the onset of maternal care. In a sense, the role of oxytocin in the uterus and mammary tissue for providing the physiological support of the offspring is matched by a role in the brain for subserving the motivational changes essential for maternal care.

Estrogen is critical to the regulation of oxytocin neurotransmission. In fact, the steroid treatment regimen designed to artificially facilitate rat maternal behavior (13 days of estrogen and progesterone followed by 2 days of estrogen alone) has recently been shown to be the ideal schedule for inducing oxytocin gene expression in the hypothalamus (45). In addition, estrogen regulates the number of oxytocin receptors, not only in the uterus and mammary myoepithelium but also in a few discrete nuclei in the brain (reviewed in reference 12). The physiological changes in gonadal steroids that occur during pregnancy appear to be sufficient in view of the fact that oxytocin receptors increase in two key limbic brain regions—the bed nucleus of the stria terminalis and the ventromedial nucleus of the hypothalamus—at or just before parturition, coincident with the onset of maternal behavior (46) (figure 5).

The available data suggest a model in which oxytocin essentially transduces the physiological changes in gonadal steroids by amplifying both production of peptide and number of receptors. The changes in oxytocin receptors are not ubiquitous. Only those regions rich in estrogen receptors (e.g., the bed nucleus of the stria terminalis and the ventromedial nucleus of the hypothalamus) show increased oxytocin receptor binding, but in these regions the changes are rapid and profound (up to 300% increases in hypothalamic binding in 72 hours) (47). Other brain regions with oxytocin receptors fail to concentrate estradiol (48). Thus, in select target sites, the sensitivity to endogenous oxytocin increases markedly at parturition. These regions appear to be critical for the onset of maternal behavior. Females without this increase in oxytocin neurotransmission may exhibit normal labor but fail to care for their offspring (12).

It is important to recognize that oxytocin is only one link in a very complex neurochemical chain necessary for maternal behavior. It is not yet clear how oxytocin influences other neurotransmitters or even if it functions to increase or decrease neural activity (49). Research using site-specific injections of an oxytocin antagonist suggests that the peptide may be particularly important for regulating dopaminergic function from the ventral tegmental area (50). Indeed, dopamine has also been implicated in certain aspects of rat maternal behavior (51, 52). Oxytocin, either through dopamine or by a direct effect, may also regulate prolactin and

FIGURE 5. Model of Effects of Oxytocin on Maternal Behavior in the Laboratory Rat[a]



[a]The available data suggest that oxytocin influences parallel targets in the brain and peripheral organs. Parvicellular neurons in the paraventricular nucleus project to distant neural sites. Either by axonal transport or by CSF, oxytocin influences limbic targets labeled by specific receptors. These sites have been implicated in the initiation of maternal behavior. Pituitary release of oxytocin into plasma results in contraction of mammary myoepithelium (milk ejection) and uterine myometrium (labor and delivery). The keys to understanding this model are gonadal steroids (estrogen and progesterone), which increase synthesis of oxytocin in the paraventricular nucleus and supraoptic nucleus, increase release of oxytocin both centrally and peripherally, and dramatically increase oxytocin receptors in steroid-concentrating regions of the brain, including the bed nucleus of the stria terminalis (BNST), the ventromedial nucleus of the hypothalamus (VMN), and possibly the medial preoptic area (MPOA), as well as in peripheral organs (mammary and uterine tissue). The induction of oxytocin receptors by estrogen is so rapid and profound that this receptor can be thought of as a transducer of physiological changes in steroid levels for cycling or pregnant females.

opiate release, two other neuropeptide systems that appear to influence maternal behavior (53, 54).

What about paternal behavior? Paternal behavior is minimal in rats, so there has been relatively little study of its neural basis. Paternal care is a more robust phenomenon in monogamous species, such as the prairie vole. In one study of male prairie voles, vasopressin injected directly into the lateral septum increased the time a male spent with a pup (55). A selective vasopressin antagonist injected into the same region decreased paternal care (55). In the prairie vole, the innervation of the lateral septum is much greater in males than females (56). Following exposure to a pup, the content of vasopressin in this region decreases, probably as a result of peptide release (57). Pup exposure (and testosterone treatment) also increases vasopressin gene expression in male prairie voles in the bed nucleus of the stria terminalis—the very region implicated in female parental care in the rat (58).

In summary, oxytocin has been implicated in the onset of maternal behavior in the rat, and vasopressin appears to influence paternal behavior in the prairie vole. As with pair bonding behaviors, the mechanisms by which these peptides influence parental behaviors remain speculative. With both peptides, however, gonadal steroids appear to be critical for effects on parental behavior.

In humans, pituitary oxytocin is secreted into the circulation during parturition and nursing. Based on the data from other mammals, one might speculate that the central release of these peptides during labor or nursing contributes to the affiliative bond formed between mother and infant. Clearly, however, human maternal behavior, in contrast to maternal behavior in rats or sheep, does not commence at parturition and does not require either labor or nursing. In our own species, one might conclude that oxytocin is not necessary for the initiation of maternal behavior (reference 59, for instance). On the other hand, there are women who appear not to bond to their infants after normal deliveries. One hypothetical mechanism could be a deficit in CNS oxytocin neurotransmission—as occurs in animal studies with central oxytocin antagonist administration. Such a deficit might result from a mutation of the oxytocin or vasopressin receptor.

There are four known classes of neurohypophyseal hormone receptors: oxytocin, vasopressin 1a (in the brain), vasopressin 1b (in the pituitary), and vasopressin 2 (in the kidney). Several pedigrees have been described with mutations of the vasopressin 2 receptor and resultant nephrogenic diabetes insipidus (60). Whether women with a defective oxytocin receptor or men with a defective vasopressin 1a receptor would show deficits in parental care remains to be demonstrated.

INFANT ATTACHMENT

The study of attachment in infancy forms the basis of most of what we know about the behavioral process of bonding. Studies of imprinting in birds (61), early olfactory learning in rabbits (62), and the development of affectional bonds in nonhuman primates (63) have yielded a rich literature on the process by which the newborn forms a selective attachment to its mother. Two insights are particularly promising in this field. Smotherman and Robinson (64) have described the prenatal capacity for learning in rats. Not only does the rat fetus demonstrate classical conditioning (65), but this form of conditioning appears to be dependent on an opiate mechanism (66). This observation suggests that many of the affectional ties to the mother observed postnatally could be laid down by prenatal experience, as one might expect from the observation that newborn human infants respond selectively to the sound of their mother's voice (67).

In addition, Hofer and his colleagues (68) have demonstrated that the process of mother-infant attachment, which superficially appears relatively simple in a rat, actually involves several independent physiological processes in which the mother serves as a "hidden regulator" for the infant. In a sense, this early postnatal period might be considered as "extra-uterine gestation" in that the infant's heart rate, respiratory rate, rate of protein synthesis, and endocrine status are under subtle but pervasive maternal control. What is particularly fascinating about this model is the implication that dysregulation between mother and infant could occur in a discrete aspect of function even though there is no loss or separation apparent. That is, if a rat mother fails to groom her infant, the pup might show a decreased rate of protein synthesis but a normal heart rate and normal corticosterone concentration (69). Conversely, nongrooming maternal contact appears to be critical for stabilizing corticosterone but not for several other physiological measures (70). The way in which maternal behavior and infant physiology interact is no doubt reciprocal and largely dependent on the infant's stage of development. In a broader sense, mammalian infant attachment, unlike imprinting in birds, is not a singular, instantaneous event but a complex of various behavioral-physiological interactions beginning prenatally and evolving postnatally.

Vasopressin and oxytocin are both found early in development, although in the rat, oxytocin does not show a fully processed transcript until the postnatal period (71). Receptors for both peptides are found in the developing brain (72–74). Indeed, there is a transient but marked "overproduction" (relative to the adult) of both oxytocin and vasopressin receptors in limbic brain areas in the first 2 postnatal weeks (in both rodents and primates). Although these binding sites are particularly enriched in the cingulate cortex (a region implicated in separation distress), we do not know if these putative receptors are functional; nor do we know why they disappear by the time of weaning. Exogenous administration of oxytocin or vasopressin reduces the separation response of the rat pup, consistent with the possibility that these binding sites are responsive to their respective peptides and that these peptides have a role in either attachment or the separation response (75, 76).

It might be assumed that oxytocin, which is secreted in high concentration into breast milk (77), could also quiet the infant by being absorbed through the neonatal gut and transported into the brain. This idea seems intuitively appealing, but there are few data to support or refute it. Perhaps the most intriguing evidence implicating oxytocin in the infant's attachment response comes from a recent study demonstrating that oxytocin facilitates a rapid conditioned association to maternal odor cues but not to nonsocial stimuli (78). An oxytocin antagonist actually delays this form of conditioning. These studies suggest that oxytocin specifically serves a function related to infant attachment to the mother, linking cues in the environment to the infant's memory of the mother.

Synthetic oxytocin (Pitocin) is administered intravenously to support uterine contraction in most deliveries. Although oxytocin has a brief plasma half-life in the adult and does not cross the mature blood-brain barrier, its fate and distribution in the human neonate is not known. Even if 1% of the administered dose of oxytocin enters the brain, this could increase physiological concentrations by several-fold in both the mother and the infant. It is surprising that so little research has been done on the effects of this routine treatment on the emerging mother-infant relationship.

ATTACHMENT OR ATTACHMENTS

The foregoing discussion focuses on oxytocin and vasopressin, but the reader should not assume that these two neurohypophyseal peptides are either unique or independent. Several other neurochemical systems have been implicated in maternal behavior (prolactin, opioids, dopamine, γ-aminobutyric acid [GABA]) (reviewed in reference 43) and infant attachment (GABA, opioids, serotonin) (reference 79, for instance). A study of allogrooming, the prototype of affiliative behavior, in nonhuman primates suggests an important role for one of the brain opioid systems in both the response to being groomed and the initiation of grooming behavior (80). A recent report described the absence of maternal care in mice lacking the immediate early gene fos-B, which may serve as an intracellular messenger for several different neurotransmitters (81). All of these studies focused on one neurochemical at a time, while recognizing that none of these agents works in isolation. For instance, oxytocin receptors are specifically localized to pituitary lactotrophs (82), opiates regulate oxytocin release (83), and both oxytocin and vasopressin influence a broad set of autonomic targets in the brainstem (84). Many of these interactions occur in a regionally specific fashion, depending on the presence of receptors or the influence of relevant transcription factors such as estrogen or androgen receptors.

In a sense, then, oxytocin and vasopressin provide interesting case studies for investigating the neural substrates of attachment, but neither peptide should be thought of as prepotent or even preeminent for these behaviors. These peptides are not exclusively "attachment hormones," and it seems likely that future research will reveal that they are not unique in their effects. Their involvement in several different forms of attachment, however, from infant quiescence to parental care to pair bonding, raises an interesting question. Are these various forms of attachment simply different behavioral manifestations of a single neural pathway that mediates the requisite affiliative behaviors depending on the social and endocrine context? Is there one "attachment circuit" present at birth that subserves the diverse range of attachments through the life span?

Undoubtedly, there is not a single circuit, but there are specific neural pathways that repeatedly emerge as critical for reproductive behaviors as well as attachment. Many of these regions are rich in oxytocin and vasopressin receptors. Various regions of the amygdala and the lateral septum and their projections through the bed nucleus of the stria terminalis to the rostral hypothalamus (medial preoptic area) appear important for parental and pair bonding behaviors. Pathways from the rostral hypothalamus to the ventral tegmental area may be critical for integrating social information with reward pathways, especially in highly affiliative species that respond to social stimuli as reinforcers. In the rodent, many of these nuclei involved in attachment behaviors are limbic areas that process olfactory information. In the primate, olfactory information may still have some influence, but these limbic nuclei are processing visual input as well as other sensory modalities. Most important, limbic structures in the primate brain are governed by a massive cortical mantle capable of influencing social interaction.

SUMMARY

Social attachment is a complex process involving changes in sensory, cognitive, and motor functions. Remarkably, the neurohypophyseal neuropeptides oxytocin and vasopressin appear to be important for the formation of social attachments, including pair bonding in monogamous mammals, the initiation of parental care in both males and females, and possibly some aspects of the infant's attachment behavior. Recent data are consistent with the hypothesis that these hormones render gender-specific effects—oxytocin mediates behavioral effects in females, and vasopressin mediates behavioral effects in males. Both the pathways and their regulation by gonadal steroids change markedly across species, precluding a simple extrapolation from mouse to monkey to human. Nevertheless, the available data recommend the study of these neuropeptides in the human brain, especially in disorders such as autism. Because changes in very discrete clusters of receptors appear important for regulating social behaviors in animal studies, it seems unlikely that measures of CSF or plasma hormone concentrations will be definitive in human neuropsychiatric illness. A better approach may be the study of cell bodies or receptors in postmortem

brain tissue or the search for functional variations in oxytocin or vasopressin receptor genes. The evidence from preclinical studies provides a clue of where to look and what to look for in the human brain to investigate the pathophysiology of clinical disorders of social attachment.

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