Pergamon

Psychoneuroendocrinology, Vol. 23, No. 8, pp. 779–818, 1998

Printed in Great Britain
0306-4530/98 $ - see front matter

PII: S0306-4530(98)00055-9

NEUROENDOCRINE PERSPECTIVES ON SOCIAL ATTACHMENT AND LOVE

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SUMMARY

The purpose of this paper is to review existing behavioral and neuroendocrine perspectives on social attachment and love. Both love and social attachments function to facilitate reproduction, provide a sense of safety, and reduce anxiety or stress. Because social attachment is an essential component of love, understanding attachment formation is an important step toward identifying the neurobiological substrates of love. Studies of pair bonding in monogamous rodents, such as prairie voles, and maternal attachment in precocial ungulates offer the most accessible animal models for the study of mechanisms underlying selective social attachments and the propensity to develop social bonds. Parental behavior and sexual behavior, even in the absence of selective social behaviors, are associated with the concept of love; the analysis of reproductive behaviors, which is far more extensive than our understanding of social attachment, also suggests neuroendocrine substrates for love. A review of these literatures reveals a recurrent association between high levels of activity in the hypothalamic–pituitary–adrenal (HPA) axis and the subsequent expression of social behaviors and attachments. Positive social behaviors, including social bonds, may reduce HPA axis activity, while in some cases negative social interactions can have the opposite effect. Central neuropeptides, and especially oxytocin and vasopressin have been implicated both in social bonding and in the central control of the HPA axis. In prairie voles, which show clear evidence of pair bonds, oxytocin is capable of increasing positive social behaviors and both oxytocin and social interactions reduce activity in the HPA axis. Social interactions and attachment involve endocrine systems capable of decreasing HPA reactivity and modulating the autonomic nervous system, perhaps accounting for health benefits that are attributed to loving relationships. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords—Love; Social attachment; Sex; Oxytocin; Vasopressin; Monogamy; Voles.

WHAT IS LOVE?

Attachment, commitment, intimacy, passion, grief upon separation, and jealousy are but a few of the feelings or emotions sometimes used to describe love (Hatfield and Rapson, 1993; Sternberg and Barnes, 1988). From a scientific perspective, love is a hypothetical construct with many dimensions and interpretations. However, the various emotional states and behaviors associated with love are rarely investigated. In part this is because love has been the domain of poets, novelists, and clinicians, and often is considered beyond the scope of experimental science.

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The purpose of this paper is to review behavioral, neurochemical and anatomical substrates of social attachment, and suggest possible mechanisms through which specific neuroendocrine systems may regulate social attachment. Because scientific study, and especially neurobiological research, demands rigorous experimental control and uses invasive methods, the methods of science are difficult to apply to the personal experiences associated with human love (Porges, 1998). Laboratory rodents, which are preferred subjects in neurobiological research, generally do not show selective social behaviors, and do not lend themselves to studies of love. Various primate species do show social bonds, with features that resemble love, but primates are difficult to study, especially with invasive techniques. Work on maternal bonding has taken advantage of the fact that precocial ungulates, including sheep, are excellent subjects for neurobiological investigation, and do develop selective filial attachments. In addition, monogamous mammals, including prairie voles (*Microtus ochrogaster*) develop adult heterosexual pair bonds which can be studied in the laboratory. Most research on social attachment at present comes from these animal models. In addition, parental behavior and sexual behavior share common features with attachment and are intimately associated with the concept of love. Therefore, the analysis of parental and sexual behaviors, which can be studied in a variety of species, also offers insight into the neurophysiology of love.

DEFINITIONS AND MEASUREMENTS OF LOVE AND ATTACHMENT

Love and social attachments function to facilitate reproduction, provide a sense of security and reduce feelings of stress or anxiety. The neurobiology of love is interwoven, phylogenetically and ontogenetically, and in adulthood with reproduction and homeostasis (Uvnas-Moberg, 1997).

Attachment is a component of most, if not all, definitions of human love (Bartholomew and Perlman, 1994; Sternberg and Barnes, 1988). Although attachment may exist in the absence of love, it is unlikely that love can exist in the absence of attachment. Attachment as a concept, can be operationalized and studied experimentally, and thus offers a starting point for analyzing the scientific basis of love.

Behavioral theories or models of attachment have focused on either caregiver-infant interactions or adult heterosexual pair bonding. There are similarities between the behaviors associated with parent–infant attachment and adult romantic attachments. In fact, several investigators have suggested that these types of love or attachment share common biological substrates (Fisher, 1992; Hazan and Shaver, 1987; Panksepp et al., 1997).

Attachment is commonly defined as a selective social or emotional bond (Ainsworth, 1989; Bowlby, 1969, 1973, 1980; Hennessy, 1997). Although social bonds cannot be directly measured, the concept of attachment typically has been defined by behavioral or physiological processes. Maintenance of proximity or voluntary contact with an attachment object are the most commonly used behavioral indices of attachment (Carter et al., 1995). Selective or differential behaviors, such allogrooming, directed toward the presumed object of attachment also may be measured. Attachment, especially in primates, sometimes is measured by observing the visual tracking of the attachment object (Kraemer, 1992, 1997). Behavioral tests of attachment usually juxtapose responses toward a familiar individual to those directed toward other forms of social stimuli, such as an unfamiliar conspecific.

Behavioral, endocrine or autonomic responses to separation or reunion also may correlate with or be used to index attachment. In mammals distress vocalizations may increase following separation and decline following reunion. Secretion of hormones of the HPA axis, usually cortisol or corticosterone or adrenocorticotrophic hormone (ACTH), also may follow separation from the attachment figure and HPA activity tends to decline upon reunion (Hennessy, 1997; Levine et al., 1997; Mendoza and Mason, 1997; Reite and Boccia, 1994). Behavioral and endocrine responses to separation, reunion or the presence of a stressor may be discordant or have different time courses (Levine et al., 1989). No single measure of attachment has gained universal acceptance, and existing behavioral and endocrine measures may reflect different, although in some cases related, physiological processes.

EVOLUTIONARY AND CROSS-SPECIES PERSPECTIVES ON ATTACHMENT

Survival and reproduction can depend on the ability to adapt patterns of social and reproductive behavior to environmental and social demands. Social attachments function to facilitate reproduction, provide a sense of security and reduce feelings of stress or anxiety (Fig. 1). Mammals generally are social creatures, often living and reproducing in pairs or groups. Pairs and larger groups, such as families or troops, are held together by social bonds or selective social behaviors. The expression of social behavior in general, and social attachment in particular, is species-typical and highly individualized (Carter et al., 1997).

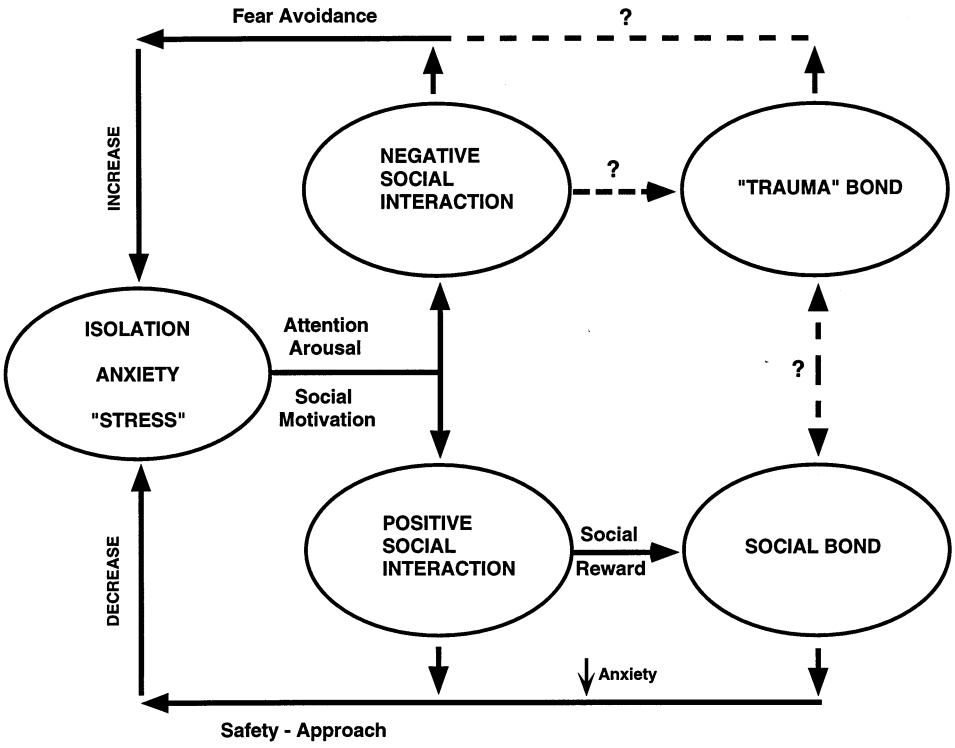

Fig. 1. Behavioral and emotional correlates of social attachment.

Table 1. Experiences or treatments associated with attachment formation

Experience or treatment	Species	Reference
Birth	Sheep	Keverne et al. (1997)
Lactation	Sheep	Keverne et al. (1997)
	Human	Uvnas-Moberg (1997)
Sexual behavior	Prairie vole	Williams et al. (1992)
Cohabitation	Prairie vole	Williams et al. (1992)
		DeVries et al. (1996)
Stressful experiences	Human	Simpson and Rholes (1994)
	Prairie vole	DeVries et al. (1996)
Corticosterone treatment	Prairie vole	DeVries et al. (1996)
Vasopressin treatment	Prairie vole	Winslow et al. (1993)
Oxytocin treatment	Sheep	Keverne and Kendrick (1992)
	Prairie vole	Williams et al. (1994)

What we now call attachment may have arisen from physiological solutions to simpler problems related to survival or reproduction (Uvnas-Moberg, 1997). Mammalian reproduction requires a particularly intense investment of maternal time and energy, and may involve commitment to a specific infant. A mammalian mother gestates her infant, she may risk her life to give birth, and then, with some human exceptions, provides postnatal care while nourishing the infant with bodily fluids. Lactation is the defining characteristic of Mammalia, and live-birth is a feature of reproduction in eutherian mammals. Hormones, including oxytocin, vasopressin, prolactin, and endogenous opiates, that are involved in sexual behavior, pregnancy, birth, lactation also have been implicated in the induction of maternal behavior and maternal attachment (Table 1). The association between social bonding and reproduction, which is most easily seen in monogamous mammals and in mother–infant interactions, may have contributed, in an evolutionary sense, to the selection of neurochemical systems involved in the occurrence of attachment behaviors. For example, pair bonding in monogamous mammals may be functionally similar to the behavioral patterns that humans associate with social attachments.

BEHAVIORAL MODELS OF SOCIAL ATTACHMENT

Basic Behavioral Systems and Attachment

The tendency to approach or avoid a particular set of social stimuli is fundamental to social behaviors, and attachment behaviors. Some stimuli may be inherently positive or may elicit positive responses; other stimuli, particularly those that are novel, can be innately aversive or fear-inducing. Studies of the physiology of positive social behaviors, including affiliative and reproductive behaviors may be especially relevant to understanding the biology of attachment. Specific physiological states can encourage positive social behaviors, including the formation of attachments and reproduction, while others may promote self-defensive or aggressive behaviors, which are generally, but perhaps not always, incompatible with attachment (Porges, 1998). Peptidergic systems involving oxytocin, and perhaps in some cases vasopressin, may serve to inhibit defensive behaviors associated with stress, anxiety or fear, and allow positive social interactions and the development of social bonds.

Adult Pair Bonds

Heterosexual pair bonds are uncommon in mammals, but are usually found in monogamous species (Kleiman, 1977). Monogamy is presumably favored under conditions when two parents are needed to rear the young, and when it confers reproductive advantages on both parents. Thus, animals that are monogamous provide an opportunity to examine the biology of selective adult social attachments in species where such bonds may facilitate survival and reproduction and, therefore, might have been favored by natural selection.

Monogamous mammals form adult pair bonds with several features that satisfy definitions of attachment and which on the surface resemble love. Monogamy in mammals does not follow taxonomic boundaries, and has been reported in various species of primates, canids and a few rodent species (Carter et al., 1995; Dewsbury, 1988; Gubernick et al., 1994; Kleiman, 1977). Experiments on the physiology of pair bonding are rare in larger mammals, and at present most of what is known regarding the neuroendocrinology of pair bonding comes from rodents.

Caregiver–infant Attachments

Attachment, especially in primates, often is studied in terms of the behavioral, emotional or hormonal changes that accompany separation from an attachment figure or reunion with or attempts to reunite with the object of an attachment. In humans and other primates, it is assumed that the attachment object, often the mother or another caretaker, serves as a secure base which is reliably available, can shield the infant from threats and may provide the infant with resources, such as food. These assumptions are the core of the theories of Bowlby (1969, 1973, 1980) and Ainsworth (1989). However, most of this literature looks at attachment from the perspective of the infant.

WHEN ARE ATTACHMENTS FORMED?

Evidence for attachment formation comes from behavioral changes associated with mammalian birth, lactation and sexual interactions (Table 1). In addition, novel or stressful experiences may encourage increased social behaviors and attachment. Comparatively high levels of HPA axis activity or other indications of sympathetic arousal, and the subsequent release of oxytocin have been measured under conditions that commonly precede or are associated with the formation of social bonds.

Birth

Mammalian birth is a uniquely stressful experience. In the mother the physiological events preceding and during parturition involve exceptionally high levels of adrenal activity and catecholamines and the subsequent release of peptides, including endogenous opioids, oxytocin and vasopressin (Keverne and Kendrick, 1992; Landgraf et al., 1991). Infants also experience parturitional stress or birth trauma and probably experience increased exposure to maternal oxytocin during labor. Hormonal experiences associated with birth may affect the tendency of young animals to form social bonds, although such effects remain to be demonstrated.

The Postpartum Period and Lactation

The postpartum period in mammals is characterized by lactation. Lactation is further associated with both maternal and infant attachment. Lactation is a dynamic process, which involves the pulsatile release of oxytocin. In addition, production of vasopressin, prolactin, and the endogenous opioids may be elevated, with concurrent reduced reactivity in the HPA axis (Altemus et al., 1995; Carter and Altemus, 1997; Lightman 1992). Lactation may provide additional opportunity for maternal bonding, perhaps allowing oxytocin to reinforce attachments initially formed during parturition.

The postpartum period and lactation also provide infants with opportunities to develop a social attachment with their mother. In addition, milk contains comparatively high levels of hormones including oxytocin (Leake et al., 1981) and prolactin (Grosvenor et al., 1990). In infants the digestive system is more permeable than in adults. There is evidence in rats that milk-borne prolactin has long-term effects on neuroendocrine development. The behavioral effects of milk-borne oxytocin have not been studied, but hormones in milk could provide another level of regulation for the developing nervous system, possibly influencing the offspring's subsequent management of stressful experiences (Carter, 1988).

Oxytocin injections, given peripherally to the mother, can facilitate nipple attachment by young rat pups, suggesting that oxytocin may change the olfactory characteristics of the parent and thus the response of a young animal to its mother (Singh and Hofer, 1978). Rats pups also show preferences for specific odors that are associated with exposure to their mothers. Preferences for the mother do not develop in animals that are pretreated with oxytocin antagonists (Nelson and Panksepp, 1996). Thus, oxytocin may act on both the mother and infant to influence the response of young animals to their mother.

Sexual Behavior and Attachment

In species that form heterosexual pair bonds, including prairie voles, sexual interactions are associated with the formation of social attachments (Carter et al., 1995). Sexual behavior also can be physiologically stressful for both sexes. Adrenal steroids, vasopressin, oxytocin and endogenous opioids are released during sexual behavior (Carter, 1992; Meisel and Sachs, 1994; Pfaff et al., 1994).

Stressful Experiences and Attachment

Threatening situations may encourage return to a secure base or otherwise strengthen social bonds (Bowlby, 1969; Panksepp et al., 1985). The literature on human and animal behavior consistently implicates stress, threatening situations, and hormones of the HPA axis in the formation of attachments.

Stress or corticosterone facilitates pair bond formation in male prairie voles (DeVries et al., 1996). Although female prairie voles did not form pair bonds with familiar males following stressful treatments, stress did encourage the development of preferences for other females, consistent with the communal breeding pattern of this species (DeVries and Carter, unpublished data). Steroid hormones, including glucocorticoids can influence the synthesis of, release of, and/or receptors for neuropeptides. In addition, steroid and peptide hormones may regulate or interact with each other to influence behavior (Table 2).

Neophobia and Attachment

Hormones can reduce fear or behavioral inhibition and permit the expression of social behaviors, such as those necessary for pair bonding, maternal behavior (Fleming et al., 1989; McCarthy et al., 1992; Numan, 1994), or sexual behavior (Carter, 1992). The neurochemical processes that are capable of overcoming neophobia also may be needed to permit the formation of new social attachments. Prosocial behavior or social contact is facilitated and aggression is diminished following central oxytocin treatments in estrogen-treated female prairie voles (Witt et al., 1990). Increases in social contact also follow oxytocin treatment in both male and female rats (Witt et al., 1992). In addition, in sexually-naive male rats a brief (15 min) heterosexual interaction is followed by an approximate doubling of serum oxytocin levels; this change was not seen in sexually-experienced males for which this situation may have been less novel (Hillegaart et al., 1997). Oxytocin treatments may reduce anxiety as measured by exploration of a novel environment in rats (McCarthy et al., 1992; Uvnas-Moberg, 1997). In humans (Chiodera et al., 1991) and prairie voles (DeVries et al., 1997), oxytocin inhibited the secretion of glucocorticoids (Fig. 3). Social contact also can inhibit HPA axis activity in prairie voles (DeVries et al., 1995, 1996). In reproductively naive prairie voles, either oxytocin (ICV) or social contact produced a 50% decline in corticosterone, which occurred within 30–60 min. In male prairie voles either mating (Insel et al., 1995) or vasopressin treatment (Dharmadhikari et al., 1997) is associated with increased exploration in the open arm of a plus maze, a measure often considered indicative of reduced anxiety.

These findings suggest that stressful conditions and anxiety are associated with the formation of new social bonds. In addition, under a variety of conditions oxytocin and/or vasopressin may function to reduce neophobia or anxiety, while concurrently promoting positive social behaviors including social attachment.

ENDOCRINE THEORIES OF SOCIAL ATTACHMENT: OVERVIEW

Data from a variety of species and different paradigms implicate oxytocin and vasopressin in social attachment and in related prosocial and reproductive behaviors, including parental and sexual behaviors. Some, but not all, of the behavioral effects of oxytocin are

Table 2. Mechanisms through which steroids and/or peptides may influence attachment

Developmental regulation of:
species-typical traits
sexual dimorphism in nervous system
alterations in peptide sensitivity or reactivity by altering:
hormones or neurotransmitters
and/or their receptors
In adulthood:
peptide synthesis and/or release
peptide receptors and/or binding
altering behaviors that release peptides
peptide–peptide interactions
steroid–steroid interactions
steroid–peptide-neurotransmitter interactions
hormonal effects on the autonomic nervous system

similar to those seen after vasopressin treatment. In addition, vasopressin, but not oxytocin, has been associated with agonistic and territorial behaviors, including mate guarding (Winslow et al., 1993). The endogenous opioids also have been implicated in attachment and in the response to separation, but the nature of this effect is currently uncertain and beyond the scope of this review (Panksepp et al., 1997; Shapiro et al., 1989).

Reproduction and social attachment are intimately connected. Steroid hormones fluctuate throughout the reproductive life of mammals and could coordinate social behaviors, including attachment formation, with specific reproductive events. Thus, hormones of the hypothalamic–pituitary–gonadal (HPG) axis are candidates for roles in the physiology of attachment. However, at present there is no evidence of a direct role for HPG axis hormones in the initiation of social attachments (Carter et al., 1995, 1997). In contrast, hormones of the HPA axis are associated with the formation of social attachments. Evidence regarding this hypothesis will be described below.

OXYTOCIN AND VASOPRESSIN: BACKGROUND

Oxytocin and Vasopressin: Structure and Synthesis

Oxytocin and vasopressin are small peptides, consisting of nine amino acids, configured as a six amino acid ring with a three amino acid tail. Oxytocin and vasopressin differ from each other in two amino acids and may have evolved from a common ancestral peptide (Acher 1996). The gene for these two peptides occupies the same chromosome. There is abundant evidence for functional interactions among these peptides (Barberis and Tribollet, 1996; Carter et al., 1995; De Wied et al., 1993; Engelmann et al., 1996; Pedersen et al., 1992). Both oxytocin and vasopressin have been described as mammalian hormones, although structurally similar peptides, such as vasotocin, mesotocin and isotocin, are found in other vertebrates (Acher and Chauvet, 1988; Moore, 1992) and invertebrates (Van Kesteren et al., 1992).

Large, magnocellular neurons in the supraoptic nucleus (SON) and paraventricular nucleus (PVN) are the major source of circulating oxytocin and vasopressin. Oxytocin and vasopressin, in conjunction with their carrier proteins, are transported from magnocellular neurons in the SON and PVN to the posterior pituitary (hypophysis), where they are stored and secreted into the blood stream. In addition oxytocin and vasopressin are released within the central nervous system (CNS) from smaller, parvocellular neurons, located in the PVN and other brain areas. The release of peptides within the CNS and posterior pituitary can occur independently, although central and peripheral release patterns also may be coordinated (Kendrick et al., 1986).

In addition to the oxytocin that is produced in the SON and PVN, cell bodies producing oxytocinergic fibers also have been identified in the bed nucleus of the stria terminalis (BNST), the anterior commissural nucleus and the spinal cord (Sofroniew, 1983). The latter fibers terminate within the CNS or release oxytocin into the cerebrospinal fluid. Oxytocin is also produced in nonneural tissue. Oxytocin gene expression increases in the PVN and SON during lactation and around birth or under hormonal conditions that mimic birth (Crowley et al., 1995; Lightman and Young, 1987, 1989; van Tol et al., 1988).

As with oxytocin the most abundant sources of vasopressin are found in the PVN and SON. Vasopressin is synthesized and released within the nervous system by parvocellular neurons in the PVN. Vasopressinergic cell bodies also have been identified in the

suprachiasmatic nucleus (SCN), medial amygdala (MAMY), BNST and other areas of the caudal brain stem. Androgens facilitate the synthesis of vasopressin, particularly in the MAMY and lateral septum (LS) (DeVries and Villalba, 1997; Van Leeuwen et al., 1985), accounting for clear sex differences in the abundance of vasopressin in the CNS.

Receptors for Oxytocin and Vasopressin

The behavioral functions of peptides, like most other hormones, depend on their capacity to bind to specific receptors. One receptor has been identified for oxytocin, while at least three receptor subtypes are responsible for the functions of vasopressin (Barberis and Tribollet, 1996; Ostrowski, 1998). V1a receptors are found throughout the CNS and cardiovascular system. V1b receptors are most abundant in the pituitary gland, and tend to occur in low densities in the CNS, often in conjunction with oxytocin receptors. V2 receptors are most abundant in the kidney.

Within the CNS oxytocin and vasopressin receptors are found in the olfactory system, limbic–hypothalamic system, brainstem and spinal cord areas that regulate reproductive and autonomic functions. The distributions of oxytocin and vasopressin receptors within the CNS vary across development and among mammalian species (Barberis and Tribollet, 1996; Patchev and Almeida, 1995; Patchev et al., 1993; Insel et al., 1994, 1997; Wang et al., 1996, 1997; Witt et al., 1991). The densities and patterns of distribution of oxytocin binding in specific brain areas also can be influenced by steroid hormones, including estrogen, progesterone, androgens and glucocorticoids (Insel et al., 1993; Johnson, 1992; Liberzon et al., 1994; Liberzon and Young 1997; Schumacher et al., 1990; Tribollet et al., 1990; Witt et al., 1991). Patterns of vasopressin receptor binding in the CNS are similar in males and females. There is at present no evidence that adult gonadal hormones can influence patterns of vasopressin receptor distribution. However, developmental hormonal experiences can alter adult gene expression for both oxytocin and vasopressin receptors (Ostrowski, 1998). The capacity of peptides to respond to developmental processes provides a mechanism through which individual experiences could influence adult social behavior. Oxytocin and vasopressin also are capable of binding to each other's receptors (Barberis and Tribollet, 1996), further complicating the analysis of mechanisms through which oxytocin and vasopressin affect behavior.

Classic Functions of Oxytocin

Oxytocin is released peripherally from the posterior pituitary in pulses that trigger muscular contractions necessary for birth. During lactation oxytocin contracts myoepithelial tissue in the breast to produce milk let-down. In general the functions of oxytocin receptors in specific areas of the nervous system remain to be determined. However, many brain regions containing oxytocin receptors have been implicated in sensory processing, memory, behavior, reproduction and/or homeostasis. Oxytocin is particularly associated with the functions of the parasympathetic component of the autonomic nervous system (ANS) (Dreifuss et al., 1992; Sawchenko and Swanson, 1982; Swanson and Sawchenko, 1980; Uvnas-Moberg, 1994). Oxytocin also plays a role in the regulation of the HPA axis (Uvnas-Moberg, 1998) although like many of its behavioral effects, the HPA modulatory effects of oxytocin are species specific.

Classic Functions of Vasopressin

The classic functions of vasopressin also are those attributed to its peripheral actions. Vasopressin is named for its capacity to increase blood pressure and has various effects on cardiovascular function (Berecek, 1991). However, neurohypophyseal vasopressin also acts within the kidney to conserve water and thus vasopressin sometimes is called the anti-diuretic hormone (ADH). Vasopressin has many functions reflecting its capacity to be released within and acts within the CNS. Vasopressin has been implicated in attention and various forms of learning and memory (De Wied et al., 1991, 1993; Engelmann et al., 1996). In rats centrally-active vasopressin, in conjunction with CRH, determines the release of ACTH by the anterior pituitary (Whitnall, 1993). ACTH, in turn, regulates the release of glucocorticoids from the adrenal cortex. Vasopressin is a central component of the sympathetic nervous system, but also may regulate parasympathetic nervous system function (Dreifuss et al., 1992; Engelmann, et al., 1996; Porges, 1998).

HORMONAL EFFECTS ON PAIR BONDING

Prairie voles, small arvicoline rodents from the midwestern United States, have proven particularly amenable to the experimental analysis of pair bond formation. Prairie voles live in pairs and show well-defined behavioral preferences for their familiar partner (Getz et al., 1981). Pair bonding in this species is assessed by allowing an experimental animal to chose between a stimulus animal made familiar by association or cohabitation, or a comparable stranger (Carter et al., 1995). Both monogamous and nonmonogamous species of voles are found within the genus *Microtus*, allowing valuable intrageneric comparisons (Dewsbury, 1988; Insel, 1997).

Oxytocin

Reliable partner preferences can develop following a period of nonsexual cohabitation, but preferences occur more quickly when a male and female are allowed to mate (Williams et al., 1992). Mating or vaginal cervical stimulation is known to release oxytocin (Carter, 1992). In addition, we have observed increased social contact in female prairie voles treated with oxytocin (ICV) (Cho et al., in press; Witt et al., 1990) (Fig. 3). We hypothesized that the release of oxytocin might facilitate pair bonding, and this hypothesis was confirmed. In female prairie voles central oxytocin treatments hastened pair bonding; conversely oxytocin antagonists interfered with partner preference formation following either oxytocin-treatments or prolonged cohabitation (Cho et al., in press; Insel and Hulihan, 1995; Williams et al., 1994).

In female prairie voles facilitative effects of centrally-administered oxytocin on pair bonding have been seen following either chronic infusions, using a miniature osmotic pump implanted 24 h prior to exposure to a partner (Williams et al., 1994), or following acute ICV injections, given immediately prior to brief (1 h) exposure to the partner (Cho et al., in press). In addition, peripheral pulses, but not single injections of oxytocin, facilitate pair bonding in female prairie voles (Cushing and Carter, 1998). In male prairie voles acute oxytocin treatments given ICV also can facilitate partner preference formation (Cho et al., in press). These results indicate that in prairie voles exogenously administered oxytocin is capable of inducing pair bonding in both sexes. These data also support the hypothesis that for females endogenous oxytocin, released during either

mating or cohabitation, plays a role in pair bond formation. The role of endogenous oxytocin in males remains less certain, possibly because males are more dependent than females on vasopressin (Insel and Hulihan, 1995).

Vasopressin

Vasopressin can also facilitate the onset of partner preferences. In male prairie voles chronic (Winslow et al., 1993) or acute (Cho et al., in press) vasopressin treatments facilitate the selection of a particular female partner. Acute vasopressin injections also can facilitate partner preference formation in female prairie voles. Testosterone treatments can increase vasopressin synthesis and mating influences vasopressin levels in males (DeVries and Villalba, 1997), offering further support for the hypothesis that endogenous vasopressin plays a role in pair bonding in male prairie voles.

Vasopressin, at least when administered as a chronic infusion, has the added ability to induce mate guarding and territoriality in males; mate guarding in this species is important to maintaining the integrity of pair bonds, since females in estrus (even when apparently pair bonded) sometimes will mate with strangers (Carter et al., 1995). Both male and female prairie voles become aggressive following sexual experience (Getz et al., 1981; Winslow et al., 1993), however, the onset of postcopulatory aggression is less predictable and slower in females. In male prairie voles aggression usually appears within 24 h of the onset of mating, while in females mating is not necessary and defensive aggression to strangers is most reliably induced by a period of a week or more of cohabitation with a male (Bowler and Carter, unpublished data). These and other findings suggest gender differences in the role of peptides in pair bonding in this species (Carter et al., 1995).

Stress and Corticosterone

Stressful experiences facilitate the onset of partner preferences in male prairie voles (DeVries et al., 1996). Male prairie voles formed new pair bonds quickly following either exposure to a stressor (3 min of swimming) or corticosterone injections. Under comparable conditions stressed females did not form new pair bonds with males (DeVries et al., 1995), but did develop preferences for females that were present immediately following exposure to the stressor (DeVries and Carter, unpublished data). Prairie voles are both monogamous and communal. Males have no opportunity to mate within their natal family, and must leave the family to reproduce. For female prairie voles, conditions of environmental stress, could produce physiological signals encouraging a return to the security of the family nest; unlike males, females may produce litters within the natal nest (McGuire et al., 1993). Thus stress may encourage the rapid formation of social preferences in both sexes, even when the object of the attachment is not necessarily a member of the opposite sex.

Catecholamines and Pair Bonding

Based on the known functions of the catecholamines, and especially dopamine, it is likely that catecholamines are involved in pair bond formation. Dopamine agonists release oxytocin, and interactions between oxytocin and dopamine are reported in rats (Kovacs, et al., 1998; Sarnyai and Kovacs, 1994). In addition, high levels of oxytocin receptor binding have been reported in the nucleus accumbens in prairie voles, but not in montane voles (Insel and Shapiro, 1992). Preliminary studies suggest that

inhibitions of dopaminergic activity (acting on the D2 receptor) can interfere with pair bonding in prairie voles (Wang Z, personal communication). Dopamine, acting in the nucleus accumbens, is considered important for a reward system in other species. Interactions between oxytocin and catecholamines may provide a mechanism for rewarding or reinforcing pair bonding. Catecholamines, including dopamine and norepinephrine, may be necessary to activate or reward various behavioral processes, including arousal and selective attention, and also may regulate the effects of oxytocin and vasopressin in the CNS (Pedersen, 1997).

SEPARATION DISTRESS AND SOCIAL BUFFERING

Separation from an attachment figure is associated with various behavioral and physiological changes (Hennessy, 1997; Reite and Field, 1985; Reite and Boccia, 1994). In young animals vocalizations, in either the audible or ultrasonic range, often increase following separation. Measurements of these vocalizations have been used as indices of distress and may be indicative of attachment (Panksepp et al., 1997).

Physiological changes, including increased secretion of glucocorticoids and/or ACTH, cardiovascular measures or immune system parameters, also have been described following social separation in primates (Reite and Boccia, 1994). Cortisol responses have been used to assess the intensity of separation distress and/or to examine the hypothesis that the presence of a partner may provide a form of social buffering (Hennessy, 1997).

Squirrel monkeys are small New World primates that usually live in unisex groups. Behavioral changes in squirrel monkeys do occur following the removal of companions, although these responses may reflect general arousal or physiological adjustments to being alone, rather than the loss of a particular companion. A number of studies have attempted to document physiological consequences following social separation in squirrel monkeys (Hennessy, 1997; Mendoza and Mason, 1997; Mason and Mendoza, 1998). Although basal cortisol levels are very high in squirrel monkeys, procedures associated with capturing one member of a pair can further elevate cortisol levels; however, this response is not affected by the presence or absence of social companions. Thus, although squirrel monkeys appear highly social, physiological measures do not suggest selective pair bonding or stress buffering by companions.

Social separation in both male and female prairie voles is followed by an increase in glucocorticoid (corticosterone) levels (Williams and Carter, unpublished data). When reunited with a partner, corticosterone levels dropped to below baseline in previously paired males and female. However, if previously paired animals and separated animals were placed with an unfamiliar animal of the opposite sex corticosterone levels remained elevated (DeVries et al., 1995). Separation from the mother also induces increased corticosterone levels in infant prairie voles, but not montane voles. Such findings suggest that adult separation responses may be related to those seen in infants.

Experiments on separation distress have tested the capacity of peptides to prevent behavioral changes during separation. The intense calling behavior of isolated domestic chicks declines following various treatments, including injections of oxytocin/vasotocin, opioids that stimulate mu receptors, and prolactin (Panksepp et al., 1997). Opiate injections also diminish distress vocalizations in guinea pigs (Herman and Panksepp, 1987). The separation cries of infant rats did not show the predicted decline following opiate treatments (Winslow and Insel, 1991a). However, in rat pups separation cries were

inhibited by central treatments with oxytocin or vasopressin (Insel and Winslow, 1991; Winslow and Insel, 1993). In squirrel monkeys there also is evidence that both vasopressin and oxytocin are capable of reducing isolation calling, although the effects were dependent on social status and high doses of the peptides (1 or 5 μg, ICV) were necessary to obtain behavioral effects (Winslow and Insel, 1991b).

As reviewed through out this paper, oxytocin has been implicated in the formation of attachments. In addition, oxytocin is capable of regulating the HPA axis (DeVries et al., 1997; Uvnas-Moberg, 1998). The data described above suggest the hypothesis that reductions or fluctuations in oxytocin activity also might account for some of the symptoms of social separation. Oxytocin is well positioned to influence both the behavioral and autonomic symptoms that follow the loss of an attachment object.

PARENTAL BEHAVIOR

Overview

The most accepted form of enduring social bond is maternal attachment. The concept of mother love (Harlow, 1986) implies a selective behavioral response by the parent to its offspring. Because of the intimate relationship between parental responses and attachments, and the conservative nature of hormone and behavior relationships, understanding parental behavior, even in cases when the behaviors are not selectively directed to a particular infant, may provide insights into the physiological of social attachment.

Hormones that regulate birth and lactation are particularly important in caregiver-child attachments (Keverne, 1995; Keverne et al., 1997; Keverne and Kendrick, 1992). Oxytocin and to a lesser extent vasopressin have been implicated in both maternal behavior and maternal attachment. Catecholamines are involved in response to novelty, arousal, selective attention, certain kinds of learning, and may play a role in the development of attachments and/or may reinforce or reward the expression of these attachments. In addition, catecholamines, endogenous opioids and prolactin affect parental behavior, possibly by modulating the rewarding aspects of this behavior (Panksepp, 1981; Panksepp et al., 1994, 1997), or by pacing of mother–infant interactions (Bridges, 1990), or through their documented abilities to influence the release or actions of other peptides, including oxytocin (Keverne et al., 1997; Parker et al., 1991).

Parental Attachment

Selective maternal attachment has been described in sheep and other precocial ungulates, which must follow their mother at birth, (Keverne and Kendrick, 1992). In sheep maternal behavior is usually directed only toward the ewe's own lamb and unfamiliar lambs are physically rejected. Vaginal–cervical stimulation and suckling, which release both oxytocin and endogenous opioids, have been implicated in maternal bonding (Keverne et al., 1997). Oxytocin injections, can cause ewes to become attached to an unfamiliar lamb presented at the time oxytocin is released or injected. Oxytocin antagonists block filial bonding in sheep. These experiments offer clear evidence that sheep can develop selective social attachments and implicates oxytocin in this form of social bonding.

Maternal Behavior

Maternal behavior shares many behavioral features with attachment. In addition, there is striking concordance between physiological and anatomical substrates of parental behavior and those thus far implicated in filial attachment (Keverne, 1995; Keverne et al., 1997).

Mammalian parental behavior is usually measured by approach and positive caregiving behaviors directed by adult animals to young conspecifics. It has been proposed that maternal behavior is facilitated when the tendency to approach infants is stronger than the tendency to avoid infants. It is further suggested that reproductively naive rats of both sexes have an inherent tendency to avoid potentially aversive novel stimuli, such as those presumably presented by rat pups (Fleming et al., 1980, 1989; Numan, 1994). Hormones associated with birth, or other factors involved in repeated pup exposures, such as habituation to pup odors, are believed to inhibit this fear-based system, thus permitting the expression of maternal responses.

Hormones of Pregnancy and Parturition. Both maternal responses and lactation are facilitated by the hormonal events of pregnancy and birth, which include prolonged exposure to comparatively high levels of progesterone and estrogen, a subsequent dramatic prepartum decline in progesterone, and increases in oxytocin and prolactin (Bridges, 1990; Pedersen, 1997; Pedersen and Prange, 1979). However, hypotheses regarding hormonal causes of parental behavior are complicated by the fact that apparently normal parental behavior is observed in virgin females, even after removal of the ovary and uterus, as well as in males of many species (Brown, 1993; Gubernick and Nelson 1989). Thus, the experiences of pregnancy and birth may facilitate, but are not essential for, parental behavior.

Adrenal Steroids. The role of hormones of the adrenal axis in maternal behavior has received comparatively little attention. However, glucocorticoid levels rise in late pregnancy, and hormones of the HPA axis have been implicated in parturition. In human females, high levels of cortisol on days 2 or 3 postpartum were correlated with positive maternal behaviors and attitudes (Corter and Fleming, 1995; Fleming et al., 1987). Cortisol levels also were correlated with positive responses to odors from infants, suggesting a role for cortisol in sensory processes. Research in rats also provides circumstantial evidence for a role for adrenal steroids in maternal behavior (McCarthy et al., 1992).

Oxytocin. Because oxytocin is a predominantly mammalian hormone with a critical role in both birth and lactation, it was an obvious candidate for involvement in maternal attachment. In fact, over 20 years ago oxytocin was suggested as the hormone of mother love (Klopfer, 1971, 1996; Newton, 1973).

ICV treatment with oxytocin has the capacity to facilitate the onset of maternal responsiveness in virgin females, acting within 30 min or less (Pedersen, 1997; Pedersen and Prange, 1979). In this species, treatment with oxytocin antagonists (OTA) (Pedersen, 1997), antibodies to oxytocin (Fahrbach et al., 1985) or lesions of oxytocin producing neurons (Insel and Harbaugh, 1989) inhibit the induction of maternal behavior. There also is evidence that oxytocin is released in or acts upon brain areas associated with maternal behavior under conditions, such as parturition, when maternal behavior also increases (Keverne and Kendrick, 1992; Kendrick et al., 1988).

Oxytocinergic pathways that originate within the hypothalamus and project to the ventral tegmental area (VTA) are necessary for maternal behavior (Numan and Sheehan, 1997; Pedersen, 1997). Mesolimbic dopaminergic projections originating in the VTA also facilitate maternal behavior. Pedersen (1997) speculates that interactions between oxytocin and dopamine contribute to the positive effects of oxytocin on maternal behavior and serve to reinforce this behavior. Oxytocin also may modulate the release of norepinephrine, which in turn could potentiate or reinforce maternal behavior.

In rats, oxytocin also has been shown to have anxiolytic and anti-nociceptive effects (Uvnas-Moberg, 1997); these properties of oxytocin may indirectly facilitate maternal behavior by increasing tolerance for pups. These and other studies (Numan, 1994; Pedersen, 1997; Uvnas-Moberg, 1997) suggest a critical role for endogenously produced oxytocin in maternal behavior in rats.

Research on maternal behavior in rats indirectly implicates corticosterone in the behavioral effects of oxytocin. For example, in one study oxytocin injections were only effective in females that were tested ≈ 2 h after being placed in a novel environment. Oxytocin treatments given immediately upon introduction to a novel setting and those given after a 24 h habituation period did not significantly facilitate maternal behavior (Fahrbach et al., 1985). In addition, the original studies of the behavioral effects of ICV oxytocin in rats were done in animals that were later shown to have a respiratory infection; oxytocin was less effective in healthy animals (Pedersen and Prange, 1979; Pedersen et al., 1992), possibly in part because the healthier animals did not experience elevated corticosterone. Alternatively, it was suggested that the animals with respiratory infections may have been anosmic, and thus less fearful of pups. Studies by Wamboldt and Insel (1987) showed that either removal of the olfactory bulbs or anosmia induced by peripheral treatments with zinc sulfate made animals more responsive to oxytocin treatments. This study was interpreted as evidence for a role for olfactory-based neophobia in maternal behavior. However, treatments that created anosmia, including surgery or zinc sulfate infusions of the olfactory mucosa, were presumably stressful and also may have been associated with elevated glucocorticoid production. In rats, glucocorticoid receptors are present on a subset of oxytocin neurons (Jirikowski et al., 1993). Thus, it is possible that elevated adrenal hormones potentiate the behavioral effects of oxytocin in rats, possibly by increasing oxytocin receptor binding (Liberzon and Young 1997; Liberzon et al., 1994). The effects of oxytocin also might act in conjunction with anosmia to facilitate maternal behavior. Increased oxytocinergic activity or anosmia, in turn, might reduce neophobia or anxiety (Uvnas-Moberg, 1997), thus permitting the expression of maternal behavior.

In what was apparently the first experiment aimed at studying the effects of oxytocin on primate maternal behavior, two nulliparous female rhesus monkeys received ICV injections of oxytocin or saline. Oxytocin treatment was followed by an increase in the frequency of touching, watching or lip-smacking that was directed toward infants, and a decrease in agonistic yawns and facial threats directed toward the observers (Holman and Goy, 1995). These findings, although preliminary, are consistent with research from other mammals, and offer support for the hypothesis that oxytocin is capable of facilitating primate social behaviors.

Indirect evidence implicates oxytocin in human maternal behavior. Oxytocin production during breast-feeding is correlated with personality traits and behaviors generally associated with parental behavior. For example, basal levels of oxytocin are positively related to calmness, while pulsatile patterns of oxytocin production are associated with a desire to please, give and interact socially (Uvnas-Moberg et al., 1990). In one study of Swedish

women, those who had acute caesarean sections had fewer oxytocin pulses during the postpartum period and also were less likely than vaginally-delivered women to describe themselves as exhibiting a calm personality and high levels of sociality (Nissen et al., 1996). This correlational study does not distinguish cause and effect, since it is possible that calm women were less likely to require caesarean sections and/or that oxytocin pulses induced calmness or increased sociality; either case could implicate oxytocin since insufficient endogenous production of oxytocin may be associated with a need for caesarean sections. In a more experimental study, women were encouraged to place their infants to the breast immediately following birth; women whose infants made early contact with the breast, subsequently spent more time with their babies and talked more to their infants than women who did not experience this form of contact (Widstrom et al., 1990). These, and other correlational studies in humans by Uvnas-Moberg (1997, 1998), support the hypothesis that oxytocin released during labor and lactation may influence human maternal responsivity and perhaps attachment. Direct or experimental tests of this hypothesis in humans are not available.

Vasopressin. ICV vasopressin also can facilitate maternal behavior, but acts more slowly than oxytocin requiring more than 1 h to significantly affect behavior (Pedersen and Prange, 1979). Because direct effects of peptides on behavior are often rapid, the comparatively slow actions of vasopressin in the induction of maternal behavior could suggest that the observed effects are mediated by intermediary processes. Injections of a selective vasopressin receptor (V1a) antagonist can inhibit maternal behavior (Pedersen, 1997). Vasopressin-deficient Brattleboro rats show lower levels of parental care (Wideman and Murphy, 1990). In addition, vasopressinergic activity increases in the hypothalamus in late pregnancy (Caldwell et al., 1987; Landgraf et al., 1991). In monogamous prairie voles central vasopressin content in males, but not females, is elevated following mating and under conditions when male parental behavior is particularly likely (Bamshad et al., 1993, 1994; DeVries and Villalba, 1997).

SEXUAL BEHAVIOR

Sexual behavior and attachment are related, but not synonymous concepts. Sexual activity can occur in the absence of social attachment and many forms of attachment do not involve sexual behavior. In humans the most desired sexual partner often is the object of strong feelings of attachment, but exceptions may exist to this pattern.

In monogamous mammals, pair bonds provide a social matrix for sexual behavior. Mating also promotes social preferences (Williams, et al., 1992), possibly because oxytocin and/or vasopressin are released during sexual interactions (Carter, 1992). Males and females tend to show intrasexual aggression which may serve as mate guarding (Insel et al., 1995; Winslow et al., 1993). In addition, established pairs often show mating preferences for familiar partners. But even in socially monogamous or pair bonding mammals, such as prairie voles, absolute sexual exclusivity is rare and both sexes may engage in extra-pair copulations (Carter et al., 1995).

Although the expression of sexual behavior and attachment are not identical, these behaviors do share several features, possibly because they share common neuroendocrine substrates. Sex steroids have been implicated in sexual behavior in a variety of mammalian species, permitting mating and fertilization to be coordinated with gonadal functions

(Meisel and Sachs, 1994; Pfaff et al., 1994). Thus, although research on the endocrinology of sexual behavior has been focused on the effects of gonadal steroids, it is becoming evident that the strength of the relationship between gonadal steroids and reproductive behaviors varies within and among species. Interactions between the HPA and HPG axes may allow reproduction to be adapted to environmental demands. Steroid hormones alone are not adequate to explain many aspects of sexual behavior. Peptide hormones, including oxytocin and vasopressin, which are regulated in part by steroid hormones, may provide mechanisms for coordinating the appearance of sexual behavior with the demands of the social and physical environment (Carter, 1992).

MECHANISMS THROUGH WHICH PEPTIDES AND STEROIDS MAY INFLUENCE ATTACHMENT

Ontogenetic Influences on Attachment

Steroid exposures during development have the capacity to produce both structural and behavioral changes (Gorski, 1990), including changes that may alter the propensity for social behavior. For example, in prairie voles prenatal steroid treatments (either testosterone or corticosterone) are associated with an increased preference for familiar versus unfamiliar partners, while postnatal treatments with these same hormones were associated with a preference for strangers (Roberts et al., 1996). Prenatal stressors or treatments with stress hormones also can affect adult patterns of social and sexual behaviors in rats (Ward and Ward, 1986) and guinea pigs (Sachser and Kaiser, 1996) Thus social preferences, upon which attachments are formed, can be developmentally altered by stress and/or steroid hormones (Table 2).

Dramatic changes in both peptides and peptide receptor binding can be detected in the immediate postnatal period (Al-Shamma and DeVries, 1996; Tribollet et al., 1991; Wang et al., 1997). Both steroid and peptide hormones are capable of altering gene expression for peptide receptors. Thus, peptidergic systems, including oxytocin and vasopressin, can be affected by the developmental history of an organism. Peptide treatments either in development (Boer 1993; Boer et al., 1994; Meyerson et al., 1988; Swabb and Boer, 1994) or in adulthood (Poulain and Pittman, 1993) may alter the sensitivity of the nervous system to subsequent hormonal experiences. For example, in rats treatment with vasopressin during the first week of life is capable of reducing gene expression for the oxytocin receptor in the PVN during adulthood (Ostrowski, 1998; Vaccari et al., 1996). Since vasopressin is part of the HPA axis and is sensitive to androgens, this finding suggests that developmental changes associated with perinatal stress or gender-dependent androgenization could alter the subsequent sensitivity of the oxytocinergic system.

We have begun to examine more directly the hypothesis that peptides have a developmental role in social attachment (Stribley and Carter, 1998). Males, and to a much lesser extent females, that were exposed to vasopressin injections during the 1st week of life were as adults more aggressive toward intruders than were untreated animals. However, animals that were treated with either vasopressin or a vasopressin antagonist continued to show the capacity in adulthood to develop a preference for a familiar partner. Thus, the mate guarding component of monogamy, but apparently not the tendency to form social attachments, was sensitive to vasopressin during development.

In adult rats, exposure to either vasopressin or oxytocin sensitizes animals to respond behaviorally to subsequent treatments with previously ineffective doses of vasopressin (Poulain and Pittman, 1993). Steroid-peptide or peptide-peptide interactions may have long term consequences for the development of neural systems that predispose a given species (Insel, 1997) or individual within a species to form social attachments.

Sex Differences in Attachment

Although changes in gonadal hormones during adulthood have not yet been strongly implicated in adult attachment formation, the substrates for social interactions generally seem to have sexually dimorphic components.

Vasopressin content is strongly determined by androgens, although the vasopressin receptors may not be sexually dimorphic. Thus, it is likely that at least some sexually dimorphic behaviors, including aggression, are determined by the availability of vasopressin (DeVries and Villalba, 1997; Wang, 1995).

In contrast, at least in rats, the effects of oxytocin on reproductive behaviors may be influenced by sex steroids, including ovarian hormones (Caldwell 1992; Schumacher et al., 1990). Thus, for female rats the behavioral effects of oxytocin may vary according to the estrous condition of the female. Male rats also are capable of high levels of oxytocin binding and like females respond to estrogen with increased levels of oxytocin binding in the hypothalamus; testosterone also increases oxytocin binding in male rats and is more effective than estrogen in this regard (Johnson, 1992). These somewhat unexpected findings, although done in a species that does not show pair bonds, do not suggest that a sexually dimorphism in oxytocin binding is likely to explain gender differences in social behavior or social attachment.

Male and female prairie voles differ in the stimuli to which they direct social preferences (DeVries et al., 1997). Pair bonds also form more quickly and last slightly longer following separation in female versus male prairie voles. In addition, in prairie voles stressful experiences have different effects on heterosexual pair bond formation in males and females (DeVries et al., 1995, 1996). In this species, oxytocin and vasopressin treatments have regionally specific effects on neuronal activation, as indexed by cFOS expression (Gingrich et al., 1997). Treatment with oxytocin increased cFOS expression in the BNST, while vasopressin treatment was associated with increased activity in the nucleus accumbens. In prairie voles sex differences in the response to peptides also were seen in the gender-specific activational effects of vasopressin on postcopulatory aggression (Winslow et al., 1993) and exploratory behavior (Dharmadhikari et al., 1997). In male, but not female, prairie voles vasopressin injections were associated with increased cFOS in the central amygdala (CAMY) (Gingrich et al., 1997). In turn, the vasopressinergic effects on the CAMY can regulate autonomic functions at least in rats (Roozendaal et al., 1993) providing a potentially sexually dimorphic substrate for social engagement.

Species Variations in Peptide Receptors

The expression of attachment behaviors varies widely among species, and the mechanisms responsible for these behaviors also must have species-specific components. Peptide hormones, including oxytocin and vasopressin, with species-typical patterns of peptide production, receptor distributions and functions (Insel and Shapiro, 1992; Insel et al., 1997; Wang, 1995; Wang et al., 1996, 1997; Witt et al., 1991; Young et al., 1996), are particularly well positioned to influence behaviors, such as pair bonding, that vary among different species (Carter et al., 1995, 1997).

Both general patterns of oxytocin receptor expression and binding and receptor responses to steroids differ among species (Insel and Shapiro, 1992; Insel et al., 1994; Insel et al. 1997; Tribollet et al., 1992; Witt, 1997; Young et al., 1996). For example, estrogen increases oxytocin binding within the VMH in rats, but not in prairie voles (Witt et al., 1991).

Species differences in peptide receptor activity are presumably an important source of interspecific variation in the behavioral effects of oxytocin and vasopressin. Species-typical variations in peptide receptors are apparent in early development. For example, vasopressin receptor binding increased rapidly in the 2nd week of life in the LS of nonmonogamous montane voles, but not prairie voles (Wang et al., 1997). Insel et al. (1997) and Young et al. (1996) have compared the genes for oxytocin receptors in prairie voles and montane voles, and found that these receptors are virtually identical in genetic structure. However, promoter elements can regulate the expression of these receptor genes in particular tissues; subtle, but potentially important species differences in base sequences may be responsible for the interspecific variations in peptide receptor distributions. Based on rodent work, especially in voles, Wang et al. (1996) suggest that neuroendocrine systems may evolve by changes in receptor distribution rather than by restructuring the presynaptic pathway. Comparisons among related vole species with very different patterns of social behavior offer insights into the role of peptides and their receptors in species-typical social behaviors (Insel, 1997).

Ontogenetic experiences, including levels of perinatal stress and varying amounts of parent-young interaction could contribute to the development of species-typical patterns of social behavior. An example of the consequences of perinatal exposure to stress hormones again comes from work with prairie voles; in this species corticosterone treatments during the perinatal period altered both social and reproductive behaviors. In female prairie voles postnatal treatments with corticosterone were associated with an increased preference for unfamiliar partners versus siblings, lower levels of alloparenting, and increased masculinization of sexual behavior (indexed by mounting behavior in females). Stressful experiences, including the absence of the father, also inhibit alloparenting in female prairie voles from a population captured in Illinois (Roberts et al., 1997, 1998). However, even within prairie voles, intraspecific population differences exist in social behaviors, including juvenile alloparental behavior and other indices of communal breeding. Prairie voles reared from populations captured in Illinois are both monogamous and communal, while those from populations captured in Kansas show some features of monogamy, but are not communal (Roberts et al., 1998). When prairie voles were reared with both parents present, alloparental behavior was much more common in Illinois versus Kansas animals; this behavioral difference in alloparenting disappeared when animals were reared only by their mothers. Animals from both populations formed pair bonds, although voles from the Illinois population were slightly more tolerant of unfamiliar animals than were Kansas voles.

Intraspecific variation provides a model for the analysis of factors that can contribute to sociality, and more specifically to social attachment. In both cases, differences based on developmental experiences would be expressed within genetic constraints. Behavioral flexibility, such as that seen in prairie voles, and possibly mediated by peptide–steroid interactions during development, allows animals to individually adapt their social systems to accommodate early experiences and environmental demands.

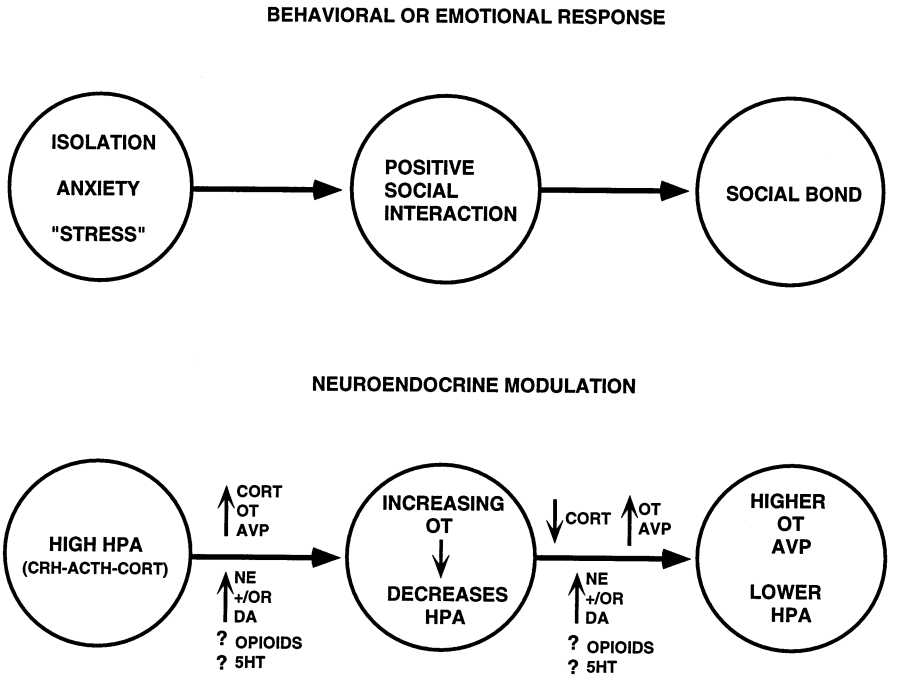

Fig. 2. Behavioral, emotional and neuroendocrine correlates of social attachment. HPA, hypothalamic–pituitary–adrenal axis; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; CORT, glucocorticoids including corticosterone and cortisol; OT, oxytocin; AVP, arginine vasopressin; opioids, endogenous opioids; 5HT, serotonin.

Species Variation in Adrenal Corticoids

Species differences in the tendency to form social bonds also may be related to variations in HPA axis activity. For example, prairie voles have serum levels of adrenal corticoids that are 5–10 × those found in nonmonogamous montane voles (Carter et al., 1995; Taymans et al., 1997). Marmosets and tamarins, which form pair bonds, also have exceptionally high levels of adrenal corticoids (Chrousos et al., 1982). Squirrel monkeys also have elevated basal corticosteroids (Hennessy, 1997; Mendoza and Mason, 1997); although squirrel monkeys do not form heterosexual pair bonds, they do form cohesive same-sex social groups. Guinea pigs can secrete very high levels of adrenal corticoids under stress, and, although not considered monogamous, also are capable of developing social attachments. In fact in male guinea pigs, death, possibly mediated by changes in the ANS, has been observed when social stress is followed by subsequent isolation from a specific social partner (Sachser and Lick, 1989, 1991; Sachser, et al., 1998).

Not all pair bonding species have exceptional levels of adrenal corticoids. For example, monogamous titi monkeys do not seem to fit this pattern (Mendoza and Mason, 1997; Mason and Mendoza, 1998). However, in many cases exceptionally high levels of activity in the HPA axis, measured as increased glucocorticoid secretion, are associated with or precede well-defined patterns of social attachment. Correlations between HPA axis activity and attachment offer support for a role for hormones of the HPA axis, and specifically the glucocorticoids in the events which eventually lead to pair bonding (Fig. 2).

STEROID–PEPTIDE INTERACTIONS

Steroid effects on peptide production. Oxytocin synthesis and release are sensitive to gonadal steroids, including estrogens and androgens (Caldwell, 1992; Rhodes et al., 1981). For example, an estrogen-sensitive promotor has been identified on the oxytocin gene (Zingg et al., 1995). Treatment with a regimen of ovarian steroids that approximates the hormonal profile during late pregnancy and near the time of parturition (chronic estrogen and progesterone followed by progesterone withdrawal) increases oxytocin gene expression in rats (Crowley et al., 1995). Glucocorticoid levels also are high in late pregnancy and may decline at delivery. Progesterone and the glucocorticoids have similar chemical structures and share many physiological and behavioral properties, and in some cases have similar affects on peptide binding (Patchev et al., 1993); these steroids could act separately or in concert to influence behavior.

Vasopressin synthesis, especially within the MAMY and BNST, is increased by androgens, producing a sexually dimorphic distribution of vasopressin, especially in neural processes that project to the LS (DeVries and Villalba, 1997; Wang, 1995; Wang and DeVries, 1994; Wang et al., 1994). Vasopressin content, detected by immunocytochemistry, declines slowly after castration, with a time course that resembles the postcastrational lose of sexual interest in male rats. In many cases the effects of androgen require aromatization to estrogen, and it is often difficult to determine the relative contributions of estrogens and androgens.

Steroid Effects on Peptide Receptors

Steroid hormones can influence oxytocin receptor binding in the CNS, particularly in the olfactory–limbic–hypothalamic axis, which has been implicated in social and sexual behaviors (Johnson, 1992). For example, there is recent evidence that progesterone is capable of binding to the rat oxytocin receptor on membranes and thus inhibiting the functions of the oxytocin receptor (Grazzini et al., 1998). This effect was highly specific and not observed following treatment with estrogen or the synthetic glucocorticoid, dexamethasone. In addition, this effect was species specific, since human oxytocin receptors, expressed in a cell line, were inhibited by a progesterone metabolite (5 beta-dihydroprogesterone), but not by progesterone itself.

The concurrent presence of multiple steroid and peptide receptors in a given neural system, or even within the same cell, offers mechanisms through which steroid hormones may regulate peptidergic functions (Axelson and Van Leeuwen, 1990; DeVries and Villalba, 1997; Jirikowski et al., 1993). In rats, gonadal and/or adrenal steroids also can cause an increase in hippocampus (Liberzon et al., 1994; Liberzon and Young 1997), and in some, but not all areas of the hypothalamus (Patchev et al., 1993). For example, pretreatment with a synthetic glucocorticoid (dexamethasone) increased oxytocin receptor ligand binding in the BNST, LS and AMY, but decreased binding in the ventromedial hypothalamus. Site-specific modulation of peptide binding by specific steroid hormones or combinations of steroid hormones could account for at least some of the regulatory effects of steroids or stress on maternal and sexual behavior.

Steroid Effects on the Production of Co-localized Peptides

Oxytocin and vasopressin are commonly co-localized with other peptides. For example, in rats corticotropin releasing hormone (CRH), cholecystokinin (CCK) and dynorphin

have been observed in magnocellular oxytocinergic neurons, while angiotensin II, galanin and dynorphin are found in vasopressinergic neurons (Levin and Sawchenko, 1993; Meister et al., 1990). The production of these additional peptides is steroid-dependent and provides a mechanism through which steroids may modulate the functions of oxytocin and vasopressin.

Behavior as an Intermediary in Steroid–peptide Interactions

Steroid hormones also may act on behavioral systems which in turn regulate the release of neuropeptides. For example, estrogen increases female sexual behavior (Pfaff et al., 1994), while androgens, in some cases converted to estrogen, increase male sexual behavior (Meisel and Sachs, 1994). Sexual behavior, in turn, can release oxytocin and vasopressin (Carter, 1992; Kendrick and Keverne, 1989). Nonsexual social contact and other forms of somatosensory stimulation also are capable of releasing oxytocin and other peptides (Uvnas-Moberg, 1994, 1997, 1998), providing a possible mechanism for the formation of social attachments, such as those that accompany nonsexual cohabitation (Williams et al., 1994).

PEPTIDE–PEPTIDE INTERACTION

Oxytocin and Vasopressin

Behavioral studies indicate that some behavioral effects of oxytocin and vasopressin are similar, while in other cases these peptides are functionally antagonistic (Bohus et al., 1978; De Wied et al., 1991, 1993; Engelmann et al., 1996; Pedersen et al., 1992). For example in rats, passive avoidance (De Wied et al., 1991), and locomotor and autonomic functions (Roozendaal et al., 1993) have indicated that oxytocin and vasopressin can have either similar or apparently opposite effects.

Research on vasopressin has concentrated on the assumption that behavioral effects of this peptide are due to actions at receptors of the V1a type, while work with oxytocin has assumed that the functions of this peptide were due to effects at the oxytocin receptor. However, because oxytocin and vasopressin are similar in structure, with the exception of two amino acids, these peptides have the potential for agonistic or antagonistic interactions with each other's receptors (Carter and Altemus, 1997; Carter et al., 1995). In addition, gene expression for the V1b receptor recently has been measured in CNS areas that contain V1a and oxytocin receptors, opening the possibility for dynamic interactions with the V1b receptor (Barberis and Tribollet, 1996; Ostrowski, 1998)

De Wied et al. (1991, 1993) have suggested that an additional receptor system, beyond the well-characterized V1a and oxytocin receptors, exists and that this receptor is capable of recognizing both peptides. For example, the role of the V1b receptor in behavior remains poorly defined. Alternatively, oxytocin and vasopressin may serve as ligands for each other's receptors. Evidence from tissue culture supports this hypothesis, and also indicates that vasopressin has a strong affinity for oxytocin receptors (Barberis and Tribollet, 1996). In some cases the receptors for oxytocin and vasopressin are in different tissues, providing mechanisms through which specific functions could be regulated by either different peptides or different concentrations of a particular peptide. In addition, site-specific effects of steroids on peptide binding could specify the differential functions of vasopressin and oxytocin. Different cells of origin and patterns of endogenous release,

such as more dramatic pulses in oxytocin versus vasopressin, could affect these systems. In addition, although the full peptide molecule is usually considered necessary for the physiological functions of vasopressin and oxytocin, smaller portions or fragments of these peptides can have behavioral functions, allowing further mechanisms for cellular specification of functions (De Wied et al., 1993).

Recent research from our laboratory suggests that while either oxytocin or vasopressin is sufficient to increase social contact, both oxytocin and vasopressin are necessary to facilitate partner preference formation in prairie voles (Cho et al., in press). In this study males or female were allowed to cohabit for one h with a stimulus animal of the opposite sex and then tested for preferences for the familiar (cohabitating) partner or an otherwise comparable stranger. Using this paradigm, large doses of 100 ng (ICV) of oxytocin and vasopressin produced high levels of social contact and strong partner preferences in both male and female prairie voles. Earlier studies, using chronic treatments (osmotic minipumps) and longer periods of cohabitation had suggested that partner preference development in female prairie voles was more sensitive to oxytocin (Insel and Hulihan, 1995; Williams et al., 1994), while males responded more readily to vasopressin (Winslow et al., 1993). The methodologies in the two studies have not been compared directly. Whether the effects of oxytocin and vasopressin on pair bonding in prairie voles are due to effects on different or common receptors remains to be determined (see below).

PEPTIDES AND THE AUTONOMIC NERVOUS SYSTEM

Hormones act on the ANS to integrate attention, emotional states and social communication, with other physiological and environmental demands. The ANS is essential for social attachment and love and also contains receptors for oxytocin and vasopressin. The various subcomponents of the ANS suggest sites at which peptides such as oxytocin and vasopressin could act to regulate these behavior.

The polyvagal theory of Porges (1995, 1997) (this volume) differentiates between a phylogenetically more modern smart vagal system, which is unique to mammals, and a more primitive vegetative vagal system, found throughout the vertebrates. According to this theory, the smart and vegetative vagal systems and, in addition, the sympathetic nervous system must interact to regulate social engagement and reproductive behaviors. The smart vagus plays a role in social engagement and the appetitive components of behavior. The source nuclei of the smart vagus, the nucleus ambiguus, contain receptors for both oxytocin and vasopressin. In contrast, the phylogenetically older vegetative vagus may regulate consummatory behaviors, such as lordosis. The source nuclei for the vegetative vagus, the dorsal motor nucleus of the vagus, contains primarily oxytocin receptors. The polyvagal theory predicts that although oxytocin and vasopressin might be acting on different target tissues, both could influence emotional systems involved in autonomic functions and social attachment.

Sensory feedback to the CNS from the visceral organs travels through vagal afferents to the nucleus tractus solitarius, providing a mechanism through which oxytocin may influence visceral experiences and bodily states. Vasopressin from the PVN also communicates with the sensory part of the dorsal vagal complex. The influence of oxytocin and/or vasopressin on visceral states could influence feedback from peripheral tissues to the brain via vagal afferents. A perceived change in visceral state would result which could affect the probability that social interactions or attachments would occur.

Thus, the ANS is an important site for peptidergic effects on emotional behavior. Because functions of the brainstem and the ANS are fundamental to virtually all other behavioral states, understanding the effects of peptides on this system may be especially critical to our understanding of physiological influences on attachment. Many components of human behavior, such as motor patterns involved in sexual behavior or parenting are regulated, at least in part, by cognitive processes. However, the decision to engage in a given behavior and various mood states are strongly determined by visceral processes or autonomic states, which may in turn motivate the occurrence of specific behaviors. Peptides, including oxytocin and vasopressin, regulate these visceral state or emotional feelings.

Vasopressin also is a component of the sympathoadrenal axis, capable in rats of increasing the secretion of ACTH and thus glucocorticoids (Whitnall, 1993). Central vasopressin allows increased activity in the sympathetic nervous system and also is associated with the functions of the smart vagus, including behavioral mobilization and social communication and engagement. Centrally-active vasopressin also can raise the set-point of vagal reflexes facilitating sympathetic activity (Porges, 1997). These vasopressinergic-vagal functions might facilitate social engagement and attachment particularly under conditions of stress or states of visceral arousal.

Oxytocin has been associated with stress-reduction. In humans (Carter and Altemus, 1997; Chiodera et al., 1991; Uvnas-Moberg, 1997, 1998) and in prairie voles (DeVries et al., 1997) oxytocin, but not vasopressin, treatments inhibit sympathoadrenal activity, including the release of adrenal corticoids. The effects of oxytocin on pair bonding or other forms of social attachment may be related to the autonomic role of oxytocin in stress reduction.

A WORKING MODEL FOR THE ROLE OF STEROIDS AND NEUROPEPTIDES IN SOCIAL ATTACHMENT

Behavioral-emotional Models of Attachment

Stressful experiences (such as pregnancy and parturition), anxiety, neophobia and isolation often precede the formation of social attachments (Figs. 1 and 2). These circumstances may increase social drive or motivation and subsequent social interactions. Positive social interactions in turn could be rewarding and in species or individuals that possess the capacity to form attachment, positive social bonds would follow. Both positive social interactions and social bonds could function to provide a sense of safety and reduce anxiety or stress.

In contrast, if social interactions were negative, fear or anxiety might increase. Depending on the gender, species, history of the individual, intensity of the experience, and so forth, negative or traumatic social interactions could feed back to heighten fear or anxiety and prevent the formation of social attachments. However, under certain conditions traumatic events may result in strong social attachments. In some cases, trauma bonds, might be formed even in the absence of a concurrent reduction in anxiety or fear.

Neuroendocrine Correlates of Attachment

Traits. The propensity to form attachments is a species-typical trait. Based on somewhat limited mammalian data, it appears that social bonding is particularly common in

species, including monogamous or highly social mammals, that are glucocorticoid-insensitive and thus capable of producing exceptionally high serum levels of glucocorticoids. At present the best known animal models of glucocorticoid-insensitivity are New World primates or rodents, many of which, such as prairie voles or marmosets, also are capable of developing social attachments.

States. Attachment formation and other forms of social behavior also are state-dependent. For example, maternal–infant attachment usually follows the extreme physiological challenges associated with pregnancy and parturition. Metabolically demanding behaviors, such as sexual activity or exercise, may precede attachment formation. In addition, both glucocorticoids and oxytocin can be anxiolytic in rats (Uvnas-Moberg, 1998). High levels of steroids, opioids, oxytocin and/or vasopressin may induce a physiological process or social motivation that increases the probability of social interactions. Our research with prairie voles indicates that either oxytocin or vasopressin can increase social contact, while it appears that both peptides may be needed to allow social bonding (Cho et al., in press). In addition, serotonin or catecholamines, possibly through effects on arousal or attention, could facilitate social interactions (Fig. 2).

It has recently been shown in rats that oxytocin is capable of facilitating conditioned place preferences (Liberzon et al., 1997). In addition, oxytocin is capable of reinforcing the tendency of young rats to develop a preference for maternal odors (Nelson and Panksepp, 1996). The mechanisms underlying these effects may be shared with those responsible for the development of selective social behaviors in monogamous rodents.

Positive social interactions are associated with an increase in oxytocin and a state-dependent decline in HPA axis activity. Oxytocin is capable of facilitating both social contact and social attachment, at least in prairie voles. In addition, positive social behaviors, perhaps mediated in part through oxytocin or vasopressin, may feed back to inhibit HPA axis activity and reduce sensations of anxiety or fear.

Social interactions if negative, might cause an increase in HPA axis activity or prevent the subsequent decline in glucocorticoids that can follow positive social interactions. Intensely negative interactions or threatening experiences might reduce the probability of subsequent attachment formation or result in an avoidance of individuals associated with the negative situation. Alternatively, attachments may form in the presence of traumatic experiences. Whether such trauma bonds are due to neuroendocrine changes that are similar to those described for positive social attachments or rely on different processes, for example related to the release of exceptionally high levels of CRH, vasopressin or catecholamines, remains to be determined.

Gender and Social Attachment. Males and females often show different patterns of social behavior and especially social bonding. Females may develop social bonds more quickly than males, while pair bonding in males is more likely to include an aggressive component. In most mammals females are more likely than males to have higher basal levels of HPA axis activity and glucocorticoids. In one species, the golden hamster, in which males have higher levels of cortisol, females are notably more asocial than males. Female golden hamsters become very aggressive after mating (Carter and Schein, 1971), sometimes leading to the death of the male partner, rather than the formation of social bonds.

Research with prairie voles suggests that the neuroendocrinology of social attachments is sexually dimorphic, with males more likely than females to form heterosexual pair bonds

in the presence of a stressful experience or high levels of HPA activity. In male prairie voles the induction of aggression toward strangers, which accompanies mating and pair bonding, seems to be particularly sensitive to vasopressin. The fact that vasopressin synthesis, especially in the limbic system, is androgen-dependent makes vasopressin a particularly likely candidate for social processes that are sexually dimorphic. Thus, species-typical, gender differences may be expected in parameters of this model.

Hypotheses. Steroid–peptide interactions, involving hormones of the HPA axis, and vasopressin and oxytocin, provide neuroendocrine substrates for species-typical social behaviors and emotions. Other peptides or neurotransmitters, including for example, endogenous opioids and monoamines, may regulate social attachment by modulating the central release or effects of oxytocin and vasopressin, as well as the functions of the HPA axis. In addition, opioids and monoamines could modulate social interactions and attachment by influencing arousal, attention, motivation and reward. Several components of this system can be modified by gonadal hormones and may be sexually dimorphic.

UNEXPLORED RESEARCH QUESTIONS

The Nature of Social Attachment

Awareness that social attachment could have physiological substrates is recent, and there are far more questions than answers. For example, is attachment one process or many? Do attachments that form slowly, during long-term associations, including lactation or nonsexual cohabitation, have the same physiology as those that form quickly, for example during an acute experience, such as birth or sexual interactions? Are the mechanisms involved in the formation of a social attachment also responsible for the maintenance of the attachment? How are the physiological changes associated with social separation or social distress related to social attachment? Do social attachments formed at different ages or in different species depend on comparable or different mechanisms? Is attachment based on the same neuroendocrine substrates that regulate maternal behavior? Are the appetitive or motivational components of attachment similar to the consummatory components? Do the factors that regulate the formation of maternal attachment or pair bonds also regulate the response to the absence of a parent or partner?

Learning and Attachment

Does social attachment represent a novel class of learning, perhaps related to imprinting or other forms of prepared learning? Do processes underlying conditioned emotional responses, such as those associated with fear or avoidance, share neural substrates with social attachment?

Species Differences in the Propensity to Attachment

What are the mechanisms that allow some species to form selective social attachments, while other related species do not? Do observed species differences in steroid hormones, peptide concentrations and/or receptors account for these differences?

Peptides

With regard to attachment formation, do oxytocin and vasopressin have a similar mechanism of action? Do these peptides work on common tissues or do they have different sites of action? Do different peptide experiences convey different behavioral messages? For example, would acute exposure to oxytocin promote a search for social contact, while chronic exposure might signal social satiety or safety and reduce social motivation? Similarly, do peripherally-active versus centrally-active peptides have comparable effects? How do various peptides, including the endogenous opiates, oxytocin and vasopressin, interact with each other to influence attachment behaviors? What is the role of other hormones, peptides or neurotransmitters, for example CRH, dopamine, norepinephrine, serotonin, CCK, dynorphin, and so forth, in the regulation of these behaviors?

Steroids

What is the role of steroid hormones in the regulation of peptidergic effects on social attachment? How do various steroids including estrogen, testosterone, progesterone and corticosterone affect this system and how do they interact with each other? Are steroid hormones from the adrenal cortex particularly important in specifying the occurrence of social bonds? Are the behavioral consequences for social attachment of acute and chronic stress different?

METHODOLOGICAL ISSUES AND THE STUDY OF HORMONAL CORRELATES OF HUMAN ATTACHMENT

Although animal research supports the hypothesis that oxytocin and vasopressin may influence social attachment, very little human research directly addresses this issue. Because neurohypophyseal hormones do not readily pass the blood–brain barrier, it is generally assumed that oxytocin and vasopressin released from the posterior pituitary gland cannot easily return to the brain. Animal research, however, suggests that oxytocin and vasopressin can affect behavior through actions both within the CNS and in the periphery. To study the CNS effects of oxytocin and vasopressin the hormones must be given in relatively high doses, with potential peripheral side effects, or the peptides must be administered directly into the CNS; even in animal research this presents technical problems for behavioral studies. Intranasal preparations of oxytocin and vasopressin agonists are available and have been used in some behavioral studies, but the effectiveness of these treatments in reaching CNS peptide receptors is uncertain. At present effective, selective agonists or antagonists, that easily pass the blood–brain barrier, have not been used in behavioral studies. Blood levels of peptide hormones do not necessarily reflect central activity, and although peptides can be measured in cerebral-spinal fluid, the relevance of such studies to dynamic behaviors is limited. In addition, peptide hormone assays are technically difficult. Thus, direct knowledge of the behavioral effects of oxytocin and vasopressin has been difficult to obtain.

CLINICAL IMPLICATIONS OF A PEPTIDERGIC THEORY OF SOCIAL ATTACHMENT

The presence or absence of attachments has broad consequences across the lifespan.

Like other mammals, humans rely on positive social interactions for both safety and reproduction. It has been argued that the tendency to form pair bonds or social attachments is a universal human characteristic (Fisher, 1992; Hazan and Shaver, 1987). Social support has documented health benefits, and the absence of positive social interactions or social bonds typically is associated with both physical and mental illness (Amini et al., 1996; House et al., 1988; Klaus et al., 1995; Knox and Uvnas-Moberg, 1998; Reite and Boccia, 1994; Ryff and Singer, 1998; Sperling and Berman, 1994).

Forced social separations or the absence of social attachments can trigger stress, anxiety, fear and even depression. The behaviors and physiological changes associated with bereavement or grief are similar to those used to define depression (Reite and Boccia, 1994). Understanding the nature of physiological processes that regulate social attachment also could be of value in the treatment or prevention of disorders, such as depression or schizophrenia, which can involve dysfunctional social attachment (Kirkpatrick, 1997).

In primate (including human) infants the absence of adequate maternal care has been associated with growth retardation, social withdrawal, inadequate interpersonal relatedness and inhibited verbal communication (Harlow, 1986). This complex of symptoms has even been recognized in human development as a medical syndrome, termed Reactive Attachment Disorder of Infancy (Shaffer and Campbell, 1994). Although the concept of attachment disorder has begun to generate treatment strategies, the relationship between this disorder and normal human attachment remains to be described.

It has been proposed that autism, which can be characterized by atypical social behavior and a failure to form social attachments, may involve abnormal activity in endogenous peptidergic systems. For example, a variety of clinical studies have implicated opioids in autism (Bouvard et al., 1995). Treatment with naltrexone produces some clinical benefits and alters biochemical profiles in a subset of autistic children. More recent studies also have begun to explore the role of oxytocin in autism (Insel, 1997). Studies in autistic adults suggest that deficits in oxytocin may be correlated with some symptoms of autism (Modahl et al., 1998) and there is a report that increased gregariousness may follow oxytocin treatments. However, the possible role for either oxytocin or opioids in selective human social attachments remains unexplored.

Other neurochemicals, such as endogenous opioids, catecholamines and serotonin, also can influence the release and actions of oxytocin and vasopressin. For example, psychoactive drugs, such as Prozac, which affect serotoninergic systems, can influence

Fig. 3. (a,b) Either cohabitation or oxytocin can inhibit corticosterone secretion in male and female prairie voles; (c) oxytocin also can facilitate pair bonding in male and female prairie voles. (a) Cohabitation involved caging with an unfamiliar member of the opposite sex for 60 min prior to collection of blood. (b). In a separate study oxytocin (OT) or a control injection of the vehicle was administered by intracerebroventricular (ICV) injection 60 min prior to collection of blood. Corticosterone levels were measured by radioimmunoassay. (a,b) Animals that received OT or experienced cohabitation showed significantly lower levels of corticosterone than controls ($p < .05$). (c) Animals were treated ICV with OT or a control injection and then allowed to cohabit with an assigned partner of the opposite sex for 60 min; following this cohabitation each experimental animal was given a 3 h preference test in which they could elect to spend time with either the familiar partner or an unfamiliar, but otherwise comparable stranger. Animals receiving OT showed a significant preference for the familiar partner ($p < .05$), while control-injected animals were equally likely to select the familiar animal or a stranger (DeVries et al., 1996)

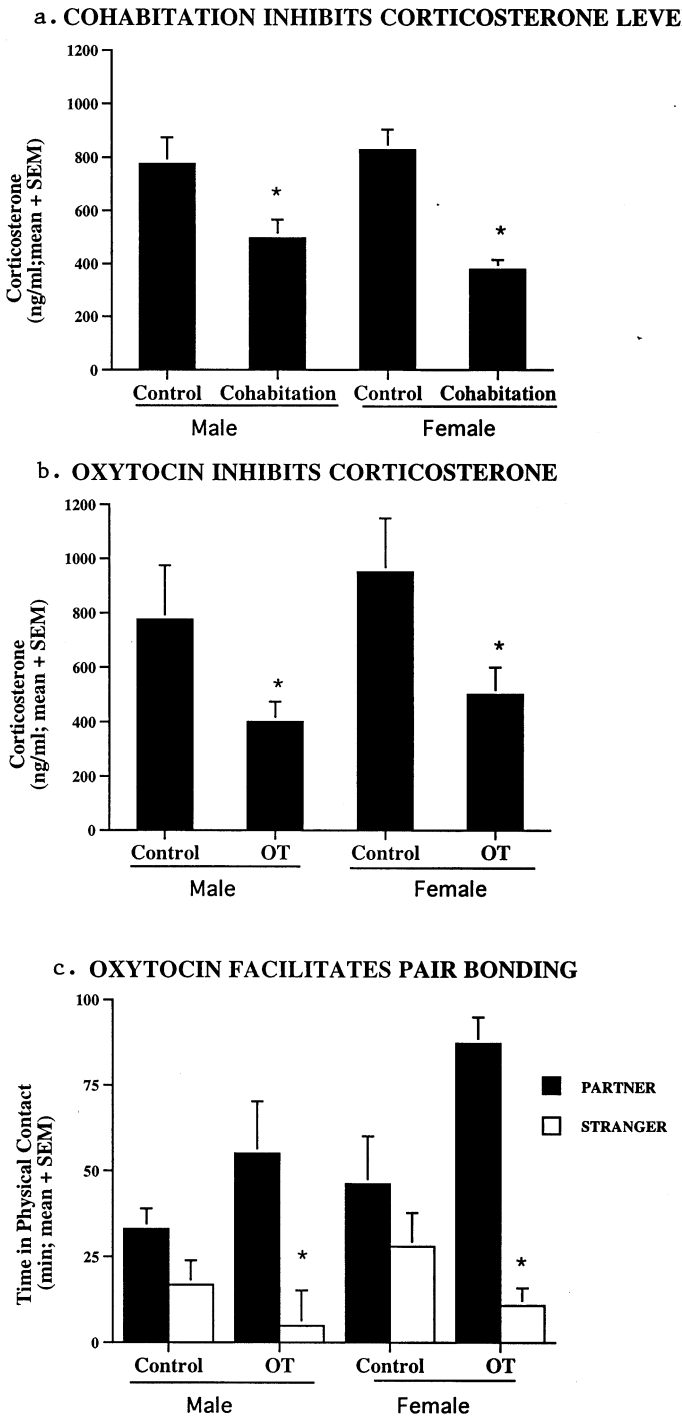
a. COHABITATION INHIBITS CORTICOSTERONE LEVELS
Corticosterone (ng/ml;mean + SEM)
1200
1000
800
600
400
200
0
*
*
Control
Cohabitation
Control
Cohabitation
Male
Female
b. OXYTOCIN INHIBITS CORTICOSTERONE
Corticosterone (ng/ml; mean + SEM)
1200
1000
800
600
400
200
0
*
*
Control
OT
Control
OT
Male
Female
c. OXYTOCIN FACILITATES PAIR BONDING
Time in Physical Contact (min; mean + SEM)
100
75
50
25
0
*
*
PARTNER
STRANGER
Control
OT
Control
OT
Male
Female

Fig. 3.

peptidergic systems (Li et al., 1993). The clinical effects of these chemicals in the context of attachment are largely unknown.

Visceral or Autonomic Sensations and Attachment

The information carried by the ANS is perceived as rather nonspecific or 'vague'. Emotional feelings have long been associated with visceral sensations, and popular culture abounds with concepts like love sickness, heartaches, and the way to a man's heart is through his stomach. Humans often express confusion regarding the source or meaning of emotional experiences, and the neurobiology of visceral experiences may be related to this perceived uncertainty. Vagal pathways in modern mammals evolved from ancient structures responsible for both oxygenating the brain and for regulating 'vegetative' functions of the digestive organs (Porges, 1995, 1997; Uvnas-Moberg, 1994, 1997, 1998). Since it is possible to measure many aspects of autonomic functions in humans, understanding the role of peptides in the ANS offers a promising window to the brain and a better understanding of emotion.

Stress and Attachment

It is well known that social attachments can form during or immediately following the experience of common threat, such as those reported by soldiers in war (Milgram, 1986). Attachments also can develop toward abusive or inadequate social partners or caretakers (Bowlby, 1969; Hatfield et al., 1989; Kraemer, 1992, 1997). A recent review of the role of stress in human attachment concludes that stressors trigger the need for proximity and attachment behaviors, and surmises that some degree of strong, yet manageable stress may be necessary for very strong bonds to form (Simpson and Rholes, 1994).

Forced isolation, anxiety, fear, and other forms of stressful conditions are associated with increased levels of HPA activity (Fig. 2). Such conditions or experiences normally tend to encourage social interactions. Both the human (Simpson and Rholes, 1994) and animal literature (reviewed here) suggests an association between HPA activation and stressful experiences and the development of social attachments. The role of hormones of the HPA axis in attachment is probably not linear, since both animals and humans under extreme conditions may become either self-protective or immobilized (Porges, 1998). Excessively stressful conditions, such as those that could compromise survival or in the face of intense grief may lead to a breakdown of social relationships (Reite and Boccia, 1994). Thus, the association between chronic or extreme stress could inhibit subsequent attachment. However, our work with rodents suggests that within a homeostatic range, stress-related physiological processes, including hormones of the HPA axis, can promote the development of social bonds (DeVries et al., 1996). In addition, positive social interactions, including social bonds, may help to create physiological states that are anxiolytic or stress reducing.

Oxytocin, perhaps released by positive social interactions, has the capacity to produce both acute and chronic reductions in the activity of the HPA axis (Carter and Altemus, 1997; Uvnas-Moberg, 1997, 1998) (Fig. 3). Studies of lactating women support this hypothesis in humans (Altemus et al., 1995). Thus, oxytocin, with both central and peripheral processes, is part of an endogenous homeostatic or in some cases anti-stress system. This system has the concurrent capacity to increase social attachment and other positive social behaviors (Fig. 3), providing the additional indirect benefits of sociality.

The role of vasopressin in human social behavior is more difficult to characterize. Vasopressin is believe to be similar to the ancestral peptide from which oxytocin and vasopressin were derived. Vasopressin binds to several types of receptors, including the oxytocin receptor. Vasopressin has been implicated in territoriality, agonistic behaviors and HPA arousal, and may be part of a more primitive adaptive system for mobilization and self-defense (Carter et al., 1995; Moore, 1992). In some cases the functions of vasopressin are apparently similar to those of oxytocin. However, as described above, under other conditions oxytocin and vasopressin may have antagonistic actions. Dynamic and complex interactions between oxytocin and vasopressin, working in the presence of a more slowly changing steroid background, could help to regulate underlie human visceral states and emotions.

Awareness of the importance of peptides, including oxytocin and vasopressin, in human behavior is comparatively recent, but of considerable importance. Many aspects of daily life can affect the release of the peptides. For example, social or sexual contact, food intake (Uvnas-Moberg, 1994), the use of steroid hormones, or drugs of abuse or alcohol (Kovacs et al., 1998; Sarnyai and Kovacs, 1994), are only a few examples of experiences that have been shown to influence the endogenous production, release or actions of these peptides. In addition, developmental research suggests various mechanisms through which peptides and steroids could retune neural systems that are implicated in attachment. Thus, peptidergic systems capable of affecting attachment, are subject to change in the face of environmental challenges.

Oxytocin and vasopressin are directly and indirectly manipulated by various medical practices. For example, large doses of 'Pitocin' a synthetic version of oxytocin, are routinely used to hasten childbirth, with unexplored effects on the social behavior or propensity to attachment of both the mother and child (Boer 1993). Long labors, caesarian-sections and the decision to breast or bottle feed are indirectly peptidergic manipulations. Remarkably little attention has been given to the behavioral or hormonal consequences of these peptide-related events which can have profound effects on behavioral, homeostatic and emotional systems for both the parent and the child (Carter 1988; DiPietro, et al., 1987; Worobey 1993).

CONCLUSIONS

The expression of attachments must incorporate genetic potentials and limitations associated with species variations, sex differences and individual experiences. Such changes require both short-term and long-lasting modifications of the nervous system. Steroids, neuropeptides and their interactions provide potential substrates for behavioral processes including those that are necessary for social attachment. Steroid hormones can regulate synthesis, release and receptor binding for oxytocin and vasopressin. These effects vary according to the species, gender and age of the subject, as well by brain region.

In mammals, rodents provide the most accessible laboratory models for physiological research. Our recent awareness of the novel physiology of monogamous rodents provides an opportunity to explore the neurobiology of attachment, and thus one aspect of love. Such studies in turn have identified important candidate systems and molecules which may be central to understanding the biology of attachment and love.

Gonadal steroids, including androgens and estrogens, have species-typical developmental effects on neural systems that have been implicated in social attachment and may

mediate both genetic and environmental influences on the propensity to form attachments. Gonadal hormones can regulate both oxytocinergic and vasopressinergic functions, and the expression of other peptides and neurotransmitters, which in turn also can modulate oxytocin and vasopressin. However, social attachments apparently can occur in the absence of gonadal steroids. At present direct evidence for an activational role for gonadal hormones in social attachment is inconclusive.

Sex differences in social behavior and the propensity to develop social attachments may reflect the organizational effects of steroids during development. High levels of vasopressinergic activity in males, regulated both developmentally and in adulthood by sex differences in androgens, could account for some gender differences in social behaviors. In addition, early exposure to vasopressin is capable of modifying subsequent aggression. Social and reproductive behaviors in males typically involve high levels of physical activity and vigilance. Vasopressin, which plays a role in pair bonding and defensive aggression, also can continue to function during mobilized behavioral states, possibly providing an explanation for male–female differences in social attachment.

There is a recurrent association between increased activity in the hypothalamic–pituitary–adrenal (HPA) axis and the subsequent expression of social behaviors and attachments. The HPA axis and adrenal steroids are particularly responsive to social and environmental demands. As described above, under certain conditions, stressful experiences and HPA axis activity are followed by increased sexual, parental and social behaviors and the formation of social bonds. Adrenal steroid–neuropeptide interactions involving oxytocin or oxytocin receptors may regulate the development of social attachments, while concurrently modulating the HPA axis. Positive social behaviors, perhaps mediated through a central oxytocinergic system, may modulate the activity of the HPA axis and the ANS, accounting for health benefits that are attributed to attachment.

Acknowledgements: I wish to acknowledge the generous advice of Stephen Porges who helped in the development of many of the organizing principles used to structure this review. I am thankful to Courtney DeVries for her help in understanding the role of the HPA axis in pair bonding, and to Bruce Cushing, Diane Witt, Leah Gavish, Luci Roberts, Mary Cho, Katie Bowler, John Stribley, Susan Taymans, Jessie Williams, Zuoxin Wang and Tom Insel for their collaborations and for allowing me in some cases to discuss their unpublished data. I am particularly grateful to Bruce Cushing and Nancy Cushing for help with the references and in finding time to complete this review and to Tom Insel for his excellent editorial comments on this manuscript. Manuscript preparation and the animal research described here from my laboratory were sponsored by the National Institutes of Health, National Institute of Mental Health, National Science Foundation and the Department of Defense.

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