



Review

Mechanisms underlying epigenetic effects of early social experience: The role of neuropeptides and steroids

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Abstract

In mammals the neonatal period is a time of significant social interaction. This is true even in solitary species as females spend a significant amount of time nursing and caring for their offspring. In social species interactions may also include the father, older siblings and extended family members. This period is a time of significant development, including organization of the central nervous system, and therefore a time when the degree and type of social interaction influences the development and expression of social behavior in adulthood. The purpose of this review is to examine the possible mechanisms for the epigenetic effects of early social experience on the subsequent expression of social behavior. We propose that social interactions during the neonatal period organize the subsequent expression of behavior by altering sensitivity to neuropeptides and steroids. Both neuropeptides (e.g. oxytocin and arginine vasopressin) and steroids (e.g. estrogen) regulate or influence the expression of behaviors such as affiliation, aggression, sociosexual behavior, parental behavior, and responses to stress. Therefore, changes in sensitivity to these hormones via reorganization of receptors or changes in hormone production and secretion are potentially powerful mechanisms through which early social experience can mold subsequent social behaviors.

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The purpose of this review is to examine how early social experience can alter the subsequent expression of social behavior in adulthood by modifying the underlying mechanisms that regulate social behavior. Genes provide the foundation of behavior, perhaps even setting the boundaries of behavioral expression, but non-genomic/epigenetic factors modify or regulate the expression of social behavior. The importance of epigenetic influences is emphasized by the recent spate of studies and review articles examining non-genomic regulation of behavior and physiology. In the last year alone, multiple reviews on the role of epigenetic factors in the establishment of social behavior and neuroendocrine systems have been published. The focus of these reviews ranged from paternal behavior and aggression (Marler et al., 2003), risk-taking behavior (Laviola et al., 2003), brain and psychiatric illness in humans (Teicher et al., 2003), to pediatric stress and subsequent dysregulation of neuroendocrine systems (Charmandari et al., 2003). While these reviews demonstrate the influence of epigenetic factors, few address the fundamental changes in the mechanisms that regulate behavior, therefore, the current review will explore the relationship between social experience during the postnatal period and the regulation of the mechanisms that control the expression of social behavior. Specifically, we will examine the evidence that early social experience can organize the response to two classes of compounds, which are critical for the expression of social behavior, neuropeptides and steroids.

There are numerous studies, using a variety of species, which indicate the importance of the social interactions in the development of behavioral and physiological responses. The following discussion is not meant to be an exhaustive review of the literature, but instead to highlight some of the relevant studies which indicate the importance of non-genomic influences on the development and expression of behavior. The influence of the social environment, begins shortly after conception and continues throughout an individual's life. Although behavior may be somewhat plastic throughout life, critical periods also exist when individuals are particularly susceptible to long-term remodeling of behavior. The first potential critical period occurs prenatally when the physiological environment of the mother/uterus can affect the subsequent expression of behavior (Clark et al., 1998; Clarke and Schneider, 1993; Schneider, 1992; Takahashi et al., 1992; Thompson, 1957). However, our purpose is to examine the effects of direct social interaction on the mechanisms that regulate social behavior and therefore this review will focus on experience during the early postnatal period.

1. Early social environments and the development of social behavior

The early postnatal period is a critical period when social interactions can affect the development of subsequent adult social behavior (Laviola and Terranova, 1998; Lovic et al.,

2001; Ladd et al., 2000; Francis et al., 1999; Chiccetti and Carlson, 1989; Suomi and Ripp, 1983), as it is a time of significant development when major modifications occur in behavior, physiology, and morphology. This period can last from several weeks to months or even years, such as in humans and some other large mammals, depending upon the species. The postnatal period is also critical for the establishment of the expression of social behavior as this is a period when learning and memory patterns, two major factors in the expression of adult social behavior, are first established (Nelson and Luciana, 2001; Stiles, 2000; Gordon, 1998).

In mammals a significant portion of the early postnatal period involves social contact, even in relatively asocial species, as the mother and offspring form an intimate bond during nursing. In addition to nursing, females also spend significant time and energy either huddling with their offspring or caring for their offspring with licking and grooming. The degree of social contact is typically higher in social mammals, where older siblings and other relatives may also spend time in direct contact with the developing infants. Finally, in monogamous species that frequently form family units, the father may spend time caring for the offspring. For example, prairie vole (*Microtus ochrogaster*) fathers huddle with the offspring when the mother is absent from the nest and spend more time in contact with pups than the female (Lonstein and De Vries, 1999; Roberts et al., 1998). Male mound building mice (*Mus spicilegus*) provide significant amounts of parental care in the form of covering the young and pup retrieval (Patris and Baudoin, 2000). In callitrichid species, tamarins and marmosets, males provide substantial parental care in the form of infant carrying, grooming, and protection (Goldizen, 1987).

Interactions with members of the social unit, especially the parent or parents, during the neonatal period are important for establishing future behavioral patterns. The relationship between early social experience and the development and expression of subsequent behavioral patterns has been examined in a number of mammalian taxa, including humans, non-human primates, and rodents. Because it is often easier to determine the effects of atypical interaction much of the work on the effects of early social experience, has concentrated on the impact of negative social interactions. For example, a lack of bonding between parents and offspring may also play a role in the expression of adult behavior. Children have an increased risk of developing anxiety or depression if they are emotionally neglected or have a cold and distant relationship with their parent (Canetti et al., 1997; Parker, 1981). Additionally, a stressful social environment that may include family conflict or harsh discipline/abuse can impact intellectual development (Trickett and McBride-Chang, 1995; Ammerman et al., 1986) and increase depression and anxiety (Gottman, 1998; Holmes and Robins, 1988). Also, abusive behavior appears to be transmitted across generations (Heyman and Slep, 2002; Pears and Capaldi, 2001).

The frequency of violence that children experience (child abuse or witness to spousal abuse) predicts violence in their own families as adults (Heyman and Slep, 2002). While the interaction of multiple factors affects the likelihood of perpetrating child abuse, such as depression and consistency of discipline as a child, parents who report childhood abuse are more likely to abuse their own children (Pears and Capaldi, 2001). While these are correlative studies, they indicate the importance of the early social environment on the establishment of behavioral patterns in adulthood.

Much of the early work on the long-term effects of social experience was done using non-human primates and was built upon Bowlby's attachment theory (Bowlby, 1969, 1973) and focused on parental loss through social deprivation or separation and subsequent depression. Studies on maternal separation began in 1960s (Kaufman and Rosenblum, 1967; Jenson and Tolman, 1962; Seay et al., 1962) and one of the first to demonstrate long-term effects of early social separation was Hinde et al. (1966) who demonstrated that a short separation of rhesus monkeys from their mothers continued to affect their interactions with their mothers weeks after being reunited. Female rhesus monkeys (*Macaca mulatta*) that are deprived, completely or partially, of maternal contact during the neonatal period, even if raised with peers, display significant changes in the expression of social behavior later in life (Suomi and Ripp, 1983; Kraemer and Clark, 1997; Kraemer, 1992; Seay et al., 1964). They are more aggressive, more likely to withdraw from novel social interactions and to abuse or neglect their own offspring than monkeys raised by their mothers. Nursery-reared rhesus monkeys show an increase in agonistic behaviors and stereotypy and a reduction in reciprocal social interactions relative to mother-reared monkeys (Winslow et al., 2003). While these studies and many others using primates indicate that the early social environment is important for the development and expression of social behavior there are limitations associated with studying humans and non-human primates. Because of the many constraints inherent in primate models, i.e. the number of subjects and breeding constraints, the possibility of genetic predisposition cannot always be ruled out and it is often difficult to elucidate the mechanisms underlying these behavioral changes. Therefore, other model systems, particularly rodents, have been used to study the effects of early social experience on the development and expression of social behavior.

In rodents, as in primates, there appears to be a strong maternal influence on the development of social behavior of their offspring. Even in guinea pigs, a species in which maternal/pup interactions are limited and the pups forage on their own shortly after birth, there is evidence that social interaction with the mother affects subsequent social behavior of the offspring. Even at an age where pups did not need milk, housing with the mother versus housing alone altered the behavior of male and female offspring (Hennessy et al., 2002), indicating that the presence or

absence of social cues is important even when contact is limited. In rats, the degree of maternal care directly impacts the development and expression of social behavior in the offspring (Boccia and Pedersen, 2001). The amount and/or type of maternal care provided are variable and this variability affects the development and expression of social behavior in the offspring. In one series of studies female rats were divided into two categories based upon how they groomed and nursed their pups; some females express high levels of licking and grooming in combination with more frequent bouts of arched backed nursing compared with other females. Females raised by high licking and grooming mothers displayed increased maternal behavior and less anxiety than females raised by low licking and grooming mothers (Francis et al., 1999). Interestingly, these results appear to be due to the type of interaction, rather than just contact between females and offspring, as there was no difference in total contact time with the pups between the two categories of mothers (Liu et al., 2000a). The response of the pups was the direct result of social experience and not due to genetic predisposition, as cross-fostered pups displayed behaviors similar to those of the foster mother rather than the genetic mother (Francis et al., 1999).

Numerous cross-fostering studies have provided insight into the role of social context in the expression of social behavior. Interspecific cross-fostering has been used to examine the formation of species-specific olfactory recognition and social preferences (Vasileva et al., 2001; Huck and Banks, 1980; McDonald and Forslund, 1978; McCarty and Southwick, 1977). The response to cross-fostering often is sexually dimorphic. Cross-fostered male lemmings (*Dicrostonyx groenlandicus* and *Lemmus trimucronatus*) showed an olfactory preference for the foster species whereas cross-fostering had no effect on female preference (Huck and Banks, 1980). Cross-fostered montane voles (*Microtus montanus*) also showed sexual dimorphism in their response, however in this species fostered males showed no preference while females preferred the foster species (McDonald and Forslund, 1978). Cross-fostering has also been used to study the development of social behavior. Mice reared by rats showed decreased aggression toward conspecifics (King, 1957; King and Gurney, 1954). In 1960 Denenberg, Zarrow and colleagues set out to study the issue of nature versus nurture, attempting to separate the genetic component of behavior from the experiential by cross-fostering mice with rats and studying the effects of the mother, pre-weaning peer group, and post-weaning peer group (Hudgens et al., 1968; Denenberg et al., 1964, 1966). The results from these studies were very interesting in that they suggested that maternal interactions have a greater impact on the subsequent expression of behavior than did the genetic contribution (Hudgens et al., 1968).

While these and other studies using rats and mice have provided significant insight into environmental influences on the development and expression of social behavior, there are two significant limitations. First, the rat social system

differs significantly from that of most human cultures, where many families consist of a male and female and older siblings and extensive social contact. Secondly, these earlier studies were limited by the use of interspecific fostering and phylogenetic differences could confound the results.

In contrast to rats there are species of rodents, such as prairie voles, that display monogamous behavior with males and females forming a long-term pair bond and providing biparental care of the offspring (Dewsbury, 1981). Studies using prairie voles and meadow voles (*Microtus pennsylvanicus*) have provided indications of the potential influence of the male/father on the social development of the offspring. Prairie voles are highly social, with both parents frequently remaining in the natal nest and rearing the offspring. Females raised to adulthood in the presence of their father displayed higher levels of alloparental behavior (Lonstein and De Vries, 2001) and older siblings that remained in the natal nest spent more time with their younger siblings if the father was present (Wang and Novak, 1994). Unlike the highly social prairie vole, meadow voles are polygynous and males and females occupy separate nests within overlapping home ranges (Madison, 1980); males do not participate in the rearing of offspring and are usually not allowed to enter the maternal nest. However, their behavior is plastic and can be manipulated to increase prosocial behavior. Meadow voles cross-fostered to prairie vole parents showed at least some biparental care, as cross-fostered males regularly entered the natal nest, while in-fostered males, raised by meadow voles, did not (McGuire, 1988). These studies clearly demonstrate that subsequent social interactions are the result of social experience, and that the presence of the father can impact the expression of social behavior.

The potential impact of the father is further supported in a study that compared the role of the father between two behaviorally distinct populations of prairie voles. One population was from Illinois which is highly social and the other from Kansas, a much less social population. Regardless of whether or not the father was present, Illinois prairie voles displayed more alloparental behavior (spontaneous care for unfamiliar juveniles); in contrast, the expression of alloparental care by Kansas prairie voles varied depending upon whether or not the father was present during rearing (Roberts et al., 1998). Roberts et al.'s (1998) findings differ slightly from those reported by Lonstein and De Vries (2001). However, these differences may have resulted from differences in the time of separation from paternal influence. In one study females were separated at weaning (Roberts et al., 1998), while in the other they remained until adulthood (Lonstein and De Vries, 2001). These results suggest several things. First, under some circumstances behavioral tendencies may be fixed genetically. Second, the timing of social experience may be important. Third, in biparental species, at least under some conditions, both parents play a role in the social development of the offspring. Finally, these studies taken

together indicate that early social environment, especially interaction with parents, affects the development and expression of behavior of the offspring and in many cases the response to social experience is sexually dimorphic.

2. Early social experience alters neuroanatomy and neuroendocrine responses

While non-genomic environmental/epigenetic effects frequently are indexed by performance, such as the degree of fearfulness, anxiety, blood pressure, stress response, tests of learning and memory, or the expression of behavior there must be underlying mechanisms that regulate the changes. Early postnatal experiences, especially those that result in long-term changes must be associated with a reorganization or restructuring of the underlying physiological/neuroendocrine mechanisms. Early studies of the effects of social experience on subsequent behavior did not examine the restructuring of the CNS, in part because of technical limitations at the time. However, more recent work has not only shed additional light on the effect of non-genomic factors on the development and expression of social behavior (Francis et al., 1999; Bester-Meredith and Marler, 2001), but have begun the process of understanding how these experiences produce changes in regulatory mechanisms (Bester-Meredith and Marler, 2001; Francis et al., 2002).

While there are limited data on the neuroendocrine effects of early social experience from humans, it is clear that early negative, socially severe experiences, can and does impact the CNS. Severe stress and maltreatment results in a reduction in the size of the mid-portions of the corpus callosum and attenuated development of the left neocortex, hippocampus, and amygdala. These developmental effects on the CNS are associated with psychiatric disease such as the development of post-traumatic stress syndrome and major depression (Teicher et al., 2003). Additional data are available from non-human primates. The first documentation of the effect of negative early experiences on brain structure was provided by Martin et al. (1991) and Siegel et al. (1993) using rhesus monkeys as a model. Significant and dramatic alterations in the chemoarchitecture of the striatum were observed 19–24 years after social deprivation (Martin et al., 1991). Complete social deprivation during the first 9 months of life resulted in a reduction in immunoreactivity for substance P, leucine-enkephalin, tyrosine hydroxylase, and calbindin in the caudate and putamen (Martin et al., 1991). Additionally, Siegel et al. (1993) demonstrated that social isolation could produce long-term alterations in neurofilament proteins associated with structural integrity of the CNS. More recent work has linked changes in behavior resulting from social deprivation with changes in neuropeptide production. The decrease in affiliative behavior observed in nursery-reared rhesus

monkeys is significantly and positively correlated with cerebrospinal oxytocin (Winslow et al., 2003).

Data from rodents continue to strengthen the evidence that early social experience alters behavior by affecting the development of neuroendocrine systems. Postnatal handling of rats resulted in changes in the responsiveness of the hypothalamic–pituitary–adrenal axis and a reduction in cell death in the hippocampus (Liu et al., 2000b; Meaney et al., 1988, 1989, 1992). The lack of cell death and retention of hippocampal size may explain why postnatally handled rats did not show the typical decrease in learning and memory associated with aging in rats, as the hippocampus is involved in certain types of learning and memory. High maternal care affects the expression of fearfulness and is correlated with changes in benzodiazepine receptors in the amygdala and α_2 adrenoceptor and corticotropin releasing hormone receptor binding in the locus coeruleus (Caldji et al., 1998, 2000). Female rat pups that were raised by high licking and grooming/high arched back nursing mothers, show increased levels of licking and grooming of their own pups in adulthood compared to females that received low levels of maternal care (Francis et al., 1999). The females raised by high licking and grooming mothers show a significant increase in oxytocin receptors (OTR), while males show a significant increase in vasopressin receptors (V_{1aR}) (Francis et al., 2002). Female offspring of high licking and grooming mothers also have increased ER α in the medial preoptic area (MPOA) and show elevated c-fos in the anterior ventral nucleus of the MPOA in response to treatment with estradiol (Champagne et al., 2003). The findings in these studies not only indicate that early social experience can alter neuroendocrine responses, they demonstrate that changes are occurring in mechanisms that are directly associated with the affected behaviors. The hypothalamic–pituitary–adrenal axis regulates the production and secretion of hormones involved in the stress response, the hippocampus is involved in learning, the locus coeruleus in fearfulness and perhaps anxiety. Arginine vasopressin (AVP) and oxytocin (OT) play a significant role in the regulation of social behavior including social memory (Ferguson et al., 2001), aggression (Bester-Meredith et al., 1999; Delville et al., 1996), and affiliation (Cushing et al., 2001; Cho et al., 1999; Young et al., 1999; Winslow et al., 1993).

3. Neuroendocrine regulation of social behavior

While factors such as context, learning, and memory play a role in the expression of social behavior, social behavior is a product of the underlying mechanisms regulating it. Social behavior often is the product of complex interactions. For example, the development of a long-term bond between two individuals may start with a slow approach and early investigation, which involves overcoming an initial fear or stress response, which may or may not stimulate aggressive

interactions. The development of social memory and recognition, the establishment of affiliative behavior, and finally the formation of a selective bond must then follow the initial interaction. Given the complexity of social interactions, many regions of the brain and a variety of neuroendocrine mechanisms may be involved (Insel and Young, 2001). Despite the potential complexity there are some major systems and hormones that play an important role in most of the behaviors associated with the expression and development of social behaviors. These include the neuropeptides AVP and OT and steroids and their interactions within a number of regions of the hypothalamus and extended amygdala (Insel and Young, 2001; Carter and Keverne, 2002; Carter et al., 1995, 1997).

3.1. Social behavior and neuropeptides: Acute and developmental effects

AVP and OT are two closely related neuropeptides that are produced in the paraventricular nuclei (PVN) and supraoptic nuclei (SON) of the hypothalamus. While produced primarily within the CNS, AVP and OT can be released either peripherally or centrally. In addition to regulating homeostatic mechanisms, central release of these neuropeptides plays a major role in regulating male and female social behavior (Cho et al., 1999; Insel and Young, 2001; Insel et al., 1998). While both compounds are produced in the PVN and SON, AVP also is produced in a number of other nuclei that are involved in regulating social behavior including the bed nucleus of the stria terminalis (BST) and the amygdala.

Both OT and AVP generally increase social behaviors such as the establishment of a pair bond and parental care. OT is involved in memory and learning (Monks et al. (2003); for review, see Engelmann et al. (1996)) and social behavior (for current review, see Carter and Keverne (2002)). Prosocial behaviors regulated by OT include the establishment or expression of social recognition and social memory (Ferguson et al., 2001; Popik et al., 1992), partner preferences (Cho et al., 1999; Cushing and Carter, 2000; Insel and Hulihan, 1995; Williams et al., 1994), female sexual behavior (Albers and Bamshad, 1998; Arletti et al., 1992; Gorzalka and Lester, 1987; Caldwell et al., 1986), and maternal behavior (Keverne and Kendrick, 1992; Pedersen et al., 1982; Pedersen and Prange, 1979). OT also regulates specific forms of aggression and has differential effects depending upon the species. OT increases maternal aggression in hamsters (Ferris et al., 1992) and decreases maternal aggression in rats (Giovannardi et al., 1998; Lubin et al., 2003). OT inhibits aggressive interactions between dominant and subordinate adult female hamsters (Harmon et al., 2002). Although many of the effects of OT are expressed primarily in females, OT also affects male behavior including social recognition (Ferguson et al., 2001), the formation of partner preferences (Cho et al., 1999) and male sexual behavior

(Witt, 1997; Arletti and Bertolini, 1985). AVP regulates scent marking (Albers and Bamshad, 1998; Winslow and Insel, 1991), grooming (Lumley et al., 2001; Drago et al., 1997; Irvin et al., 1990), social recognition (Dantzer, 1998; Dluzen et al., 1998; Greidanus and Maigret, 1996; Popik et al., 1991) and social memory (Dantzer et al., 1987), the formation of partner preferences (Cushing et al., 2001; Cho et al., 1999; Winslow et al., 1993; Insel and Hulihan, 1995), paternal behavior (Parker and Lee, 2001; De Vries and Villalba, 1997), and aggression (Albers and Bamshad, 1998; DeLeon et al., 2002; Wersinger et al., 2002; Wang et al., 1998; Ferris and Potegal, 1988).

In addition to regulating social behavior in adults, it has been hypothesized that OT and AVP have organizational effects on the CNS during early postnatal development (Wang and Young, 1997; Yoshimura et al., 1996; Boer et al., 1994; Shapiro and Insel, 1989). Neonatal manipulation of both OT and AVP can have long-lasting effects. In rats, early postnatal treatment with OT resulted in changes in weight, cholecystokinin levels, nociceptive thresholds (Uvnäs-Moberg et al., 1998), responses of aortic tissue to vasopressin (Csaba et al., 1980), and in females, placental and fetal growth during subsequent pregnancies (Sohlström et al., 2002) and sexual maturation (Withuhn et al., 2003). In prairie voles, a single intraperitoneal injection on the day of birth with OT or OT antagonist affected partner preference formation and aggression (Bales and Carter, 2003), female sociosexual behavior (Cushing et al., 2005), and stress response (Kramer et al., 2003).

There is also evidence that endogenous OT during the neonatal period has organizational effects on the expression of adult behavior. Rat pups that were licked and groomed frequently by their mothers, behaviors that may release OT in the pups (Pedersen and Boccia, 2002), showed higher levels of maternal care, less anxiety-related behavior, and expressed higher levels of central OT receptors (OTR), and higher ER α mRNA in the medial preoptic area than females raised by mothers exhibiting lower amounts of maternal care (Boccia and Pedersen, 2001; Francis et al., 2002; Champagne et al., 2003). While there are fewer studies of the neonatal effects of AVP, a role for AVP in development is also likely. In prairie voles neonatal treatment with AVP was associated with increased aggression in adult males (Stribley and Carter, 1999), while in rats early postnatal treatment with AVP produced changes in open field performance, movement, emotionality and grooming (Boer et al., 1994). Not only do postnatal manipulations of AVP alter subsequent social behavior, manipulations of the preweaning social environment alter subsequent AVP immunoreactivity (IR). Monogamous California mice (*Peromyscus californicus*) that were cross-fostered to polygynous white-footed mice (*P. leucopus*) showed decreased aggression as adults and the decrease was correlated with a reduction in AVP-IR. Cross-fostering of white-footed mice to California mice resulted in the opposite pattern; aggression and AVP were increased

(Bester-Meredith and Marler, 2001). The organizational effects of these neuropeptides are supported by other recent findings. In prairie voles treatment with OT altered neuronal activity, as indicated by c-Fos-IR, in the SON, which produces OT and AVP, and in the dorsal thalamic nucleus (Cushing et al., 2003a), which may be involved in regulating the reward aspect of prosocial behavior (Young et al., 2001). A single treatment with OT on the day of birth produced a change in the number of neurons that produce OT (females) or AVP (males) (Yamamoto et al., 2004) in the PVN by day 21. Finally, neonatal manipulations of OT significantly altered the number of cells that express ER α in the VMH and MPOA (Yamamoto et al., in press). This finding suggests that during early postnatal development neuropeptides may regulate the effects of steroids and further emphasizes the importance of studying social behavior in light of neuropeptides and E. Taken together these studies indicate that OT and AVP not only affect behavior, but also have an organizational effect on the CNS by altering the underlying mechanisms that regulate behavior.

3.2. Social behavior and ER α

Estrogen (E) is involved in the expression of sociosexual behavior in both males and females. In females E is released from the ovary into the general circulation while in males testosterone (T) is converted intracellularly by aromatase to E (Trainor and Marler, 2002). While there are a large number of gonadectomy and replacement studies that demonstrate the importance of E in regulating male and female reproduction, until recently, most of these studies did not distinguish the type of estrogen receptor (ER), α or β , that regulated or influenced the response. While ER α appears to be involved in regulating social behaviors in prairie voles (Cushing et al., 2004; Cushing and Kramer, 2005), studies using ER α KO mice have provided a detailed picture of the importance of ER α in the maintenance and expression of species-typical social behavior. ER α has been shown to play a direct role in regulating female sexual behavior, as ER α KO mice fail to mate (Rissman et al., 1999; Ogawa et al., 1998a). ER α also regulates aggression and infanticide (Ogawa et al., 1998a), locomotor activity (Ogawa et al., 2003), and has been implicated in regulating maternal behavior (Lonstein et al., 2000). Treatment of castrated male mice with T typically stimulates the display of masculine sexual behavior. However, castrated ER α KO males do not display masculine sexual behavior in response to T (Wersinger et al., 1997), suggesting that E aromatized from T plays a critical role in the expression of masculine behavior and that E is acting through ER α . In addition to playing a critical role in female reproduction, ER α influences a number of physiological aspects of male reproduction which range from regulating the distribution of CNS androgen receptors (Wersinger et al., 1997), involvement in fertility by affecting spermatogenesis through somatic support cells (Mahato et al., 2001), or

functioning of the testes (Oliveria et al., 2001). Given the importance of ER α in successful reproduction it is not surprising that ER α also influences the expression of a number of important social interactions including exploration of novel individuals (Wersinger and Rissman, 2000), partner preference (Bakker et al., 1996), aggression (Ogawa et al., 1998b), scent marking (Vagell and McGinnis, 1998), pup retrieval (Ogawa et al., 1998a) and copulatory behavior (Rissman et al., 1999; Ogawa et al., 1998a; Wood, 1996). Changes in patterns of ER α within individuals are associated with changes in the expression of prosocial behavior. For example in male mice, parental experience is associated with a change in the expression of ER α (Ehret et al., 1993). Recent studies with human males suggest that the level of male attachment and the quality of parental care/involvement can be predicted by T levels (Vagell and McGinnis, 1998). Males with lower levels of T were more responsive to cries from newborn infants (Fleming et al., 2002). Lower levels of T would suggest a reduced effect of E in males. Taken together these studies demonstrate that ER α plays a major role in regulating social behavior.

4. ER α and neuropeptides: Sexually dimorphic social behavior

A comparison of the expression of ER α between males and females reveals a relevant pattern. In rats, where adult male social activity is primarily limited to mating, the expression and distribution of ER α in the brain is similar in males and females (Kawata et al., 1998; Yokosuka et al., 1997; Kuhnemann et al., 1995; Lauber et al., 1991; Simerly et al., 1990). There are, however, some notable exceptions with males expressing significantly less ER α in the medial preoptic area (MPOA) and the ventromedial nucleus of the hypothalamus (VMH) than females. The MPOA and VMH play a major role in regulating male and female reproductive behavior, including male patterned behavior such as mounting and female lordosis (Meisel and Sachs, 1994; Yahr et al., 1994; Wood et al., 1992; Pfaff et al., 1994). The differences in these two areas suggest that E may modify sexual behavior based upon the dimorphic expression of ER α in these areas of the brain. The lack of sexual dimorphism in the other regions of the brain that express ER α is interesting, as ER α regulates not only mating behavior but also a variety of other social and sociosexual behaviors. Assuming that differences in the MPOA and the VMH account for dimorphic mating behavior, such as lordosis versus mounting, then the question becomes why is social and sociosexual behavior sexually dimorphic when many of the regions of the brain that regulate social behavior are not sexually dimorphic for ER α ? If differences in the MPOA and VMH account for differences in the sexes then it seems logical to predict that similarities in other areas should result in similar social behavior, however, this does not appear to be the case. One of the key factors in

explaining this relationship may be the expression of receptors and hormonal levels during development. It has been hypothesized that during development similar patterns of receptor expression may result in sexually dimorphic expression of behavior, while sexually dimorphic receptor expression may produce similar social behavior (De Vries and Simerly, 2002; De Vries and Boyle, 1998). During development males are typically exposed to higher levels of E than are females. Testes are active during development, producing testosterone, while ovaries produce little or no E. Males have also higher aromatase activity than females, which means that males actually have higher exposure to E during development than females. If males and females have a similar expression of ER α , then E could have a greater effect on the development of males than of females. If, in contrast, males expressed lower levels of ER α than females during development then these males would be less affected by E and develop behavioral patterns that are more similar to those of females. Findings in prairie voles, where males display high levels of prosocial behavior, support this hypothesis. A comparison of ER α during the neonatal period indicates that males express significantly lower levels of ER α -IR than females (Yamamoto et al., *in press*). Additionally, differences between males and females in early exposure or sensitivity to steroids may result in differential cell death and the establishment of sexually dimorphic expression of other hormones and receptors (for a current review, see De Vries and Simerly, 2002).

Given that ER α plays a major role in regulating social behavior, a comparison of the pattern of ER α in rats with that in a highly social species such as the prairie vole provides potential insight into the role steroids and ER α play in regulating social behavior. While both species display typical sexually dimorphic mating behaviors, males mount and females lordose, the degree of sexual dimorphism in social and sociosexual behaviors differs significantly between these species. Unlike rats, male prairie voles are highly social and display behaviors that are often associated with females, such as forming same-sex pair bonds (De Vries and Villalba, 1997; Williams et al., 1992) and long-term heterosexual pair-bonds (Getz and Carter, 1996), alloparental behavior (Roberts et al., 1998), aggression toward strange females after pair bonding (Carter and Roberts, 1997), and parental care of the offspring (Getz and Carter, 1996). Prairie voles display the same sexually dimorphic pattern of ER α expression as rats in the MPOA and the VMH, but the two species differ significantly in ER α expression in other areas, such as the bed nucleus of the stria terminalis (BST) and medial amygdala (MeA). In these areas, male prairie voles express little ER α and females express significantly higher levels while in rats males and females express similar amounts of ER α (Cushing et al., 2004; Hnatzuk et al., 1994). The BST and MeA are essential for successful reproduction and regulate a number of social behaviors (see below). The difference between rats and prairie voles in degree of sexually dimorphic ER α

expression suggests that the ability to respond to E may be critical in determining the expression of social behavior, and that a reduction in ER α in males is associated with an increase in the expression of prosocial behavior. ER α may play a role in establishing the pattern of social behavior and permit prairie voles to display a higher degree of prosocial behavior.

Responses to AVP and OT are frequently sexually dimorphic and differential responses of males and females may play a significant role in the expression of male- and female-typical behavior. The response to OT and AVP vary by species, by the behavior being regulated, and by method of treatment. In situations in which both males and females respond, the degree of response often differs between the sexes. In other situations only one sex appears to be affected. Where there are differential responses, the results suggest that OT plays a greater role in regulating female social behavior, while AVP is more important in males (Insel and Young, 2001; Insel et al., 1998). Neuropeptides differentially affect partner preference formation in males and females. In prairie voles, centrally administered OT and AVP influence the expression of partner preference in both sexes, but the dose response varies with females requiring higher doses of AVP than males (Cho et al., 1999). In contrast, only female prairie voles form a partner preference in response to peripherally administered OT (Cushing et al., 2001). There is also sexual dimorphism in the effects of OT on sexual behavior. In rats, OT can influence reproductive/mating behavior in both males and females (Arletti and Bertolini, 1985; Arletti et al., 1985). However, only females respond to treatment with prolyl-leucyl-glycinamide (Gorzalka et al., 1991), a compound that is identical to the C-terminal of OT, and which may be an active fragment produced from OT (Walter et al., 1973). In prairie voles, OT does not stimulate sexual receptivity in females (Witt et al., 1991), but it inhibits sexual activity in male prairie voles (Mahalati et al., 1991). OT and AVP also appear to affect parental behavior and aggression differentially in females and males. In rats, OT has been shown to regulate maternal behavior (Pedersen et al., 1982; Pedersen and Prange, 1979), while studies with prairie voles and deer mice indicate that AVP plays a role in the expression of paternal behavior (Bester-Meredith et al., 1999; Parker and Lee, 2001; De Vries and Villalba, 1997). In hamsters, AVP increases aggression in males but not in females (Melloni, personal communication) and OT inhibits female aggression (Harmon et al., 2002). The response of males and females to social stimuli or neonatal manipulation of peptides also indicates OT and AVP have sexually dimorphic effects. In rats high levels of maternal care resulted in an increase in OTR in females, but had no effect on V_{1a}R, while in males the same level of maternal care resulted in increases in V_{1a}R, but not OTR. Neonatal treatment with OT produced an increase in weight shortly after puberty in female, but not in male rats (Uvnäs-Moberg et al., 1998). Neonatal treatment with AVP increased

aggression in adult male prairie voles, but not females (Stribley and Carter, 1999). A single injection of OT on the day of birth altered the number of neurons in the PVN that expressed OT-IR in female prairie voles, but not in males. Taken together this results support the hypothesis that while both neuropeptides may have a role in social behavior, OT may have a greater influence in the expression of prosocial behavior in females and AVP in males (Winslow et al., 1993; Insel et al., 1998; De Vries and Villalba, 1997). These differences are particularly interesting in light of the fact that the expression of OT and AVP receptors does not appear to be sexually dimorphic, suggesting that other mechanisms maybe at play in establishing behavioral responses to these neuropeptides.

4.1. *Effects of OT and AVP are steroid-dependent*

In order to understand how the early social environment affects the development and ultimate expression of social behavior we suggest that it is critical to examine the interaction of steroids and neuropeptides. As reviewed above, there is ample evidence that both neuropeptides and steroids play a role in regulating social behavior and that experience can alter the expression or effects of these hormones. A comparison of studies examining the effects of neuropeptides with those examining E indicates that many of the behaviors being studied such as aggression (Delville et al., 1996) and partner preference formation (Cho et al., 1999; Insel and Hulihan, 1995; Bakker et al., 1996) are influenced by both neuropeptides and E (Table 1). The fact that steroids and OT or AVP have been shown to play a role in the regulation of many of the same social behaviors is not coincidental. Many of the effects of OT and AVP, especially those associated with behavior, are steroid-dependent. In females many of the effects of OT are regulated by E (Caldwell et al., 1986; Witt, 1997; McCarthy et al., 1994). In female rats, E up-regulates the expression of OTR and perhaps the production (Coirini et al., 1989; Johnson, 1992) and release (Caldwell et al., 2003) of OT. Males have higher levels of testosterone (T) than females and produce more AVP (De Vries and Villalba, 1997; De Vries et al., 1994). In adult males, steroids function to maintain the vasopressinergic system (De Vries et al., 1984, 1985). The role of T in regulating the effects of AVP in males has been demonstrated using castration studies. Removal of gonadal steroids by castration decreases the production of vasopressin in regions of the brain with ER α (De Vries et al., 1985) by reducing the synthesis of vasopressin mRNA (Miller et al., 1992). Replacing T restores AVP levels (De Vries et al., 1994; Miller et al., 1989). However, as previously discussed, T is converted to both DHT and E via enzymatic actions and recent results suggest that while DHT may play a role in AVP production, E has a greater effect on the expression of the vasopressinergic system (Han and De Vries, 2003). A further indication of the importance of E, and not androgens, in regulating the effects of OT and AVP

Table 1

Compares reported effects of the neuropeptides oxytocin and vasopressin and estrogen receptor alpha on social behavior

Behavior	Oxytocin	Arginine vasopressin	Estrogen receptor α
<i>Social behavior</i>			
Scent marking		↑ Gorzalka and Lester (1987) and Winslow and Insel (1991)	↑ Vagell and McGinnis (1998)
Social investigation			↑ Wersinger and Rissman (2000)
Social recognition and memory	↑ Ferguson et al. (2001) and Popik et al. (1992)	↑ Dantzer (1998), Dluzen et al. (1998), Greidanus and Maigret (1996), Popik et al. (1991) and Dantzer et al. (1987)	↑ Imwalle et al. (2002)
Partner preference	↑ Cho et al. (1999), Cushing and Carter (2000), Insel and Hulihan (1995) and Williams et al. (1994)	↑ Cushing et al. (2001), Cho et al. (1999), Winslow et al. (1993) and Insel and Hulihan (1995)	↑ Bakker et al. (1996)
Aggression (resident-intruder)	↓ Harmon et al. (2002)	↑ Bester-Meredith and Marler (2001), Delville et al. (1996), Albers and Bamshad (1998), DeLeon et al. (2002), Wersinger et al. (2002) and Ferris and Potegal (1988)	↑ Ogawa et al. (1998a,b), and Scordalakes and Rissman (2003)
Maternal behavior	↑ Keverne and Kendrick (1992), Pedersen et al. (1982, 1994), Pedersen and Prange (1979), and Yu et al. (1996)	↑ Wang et al. (2000)	↑ Ogawa et al. (1998a, 2003)
Paternal behavior	↑ Parker et al. (2001)	↑ Parker and Lee (2001), De Vries and Villalba (1997), Wang et al. (2000) and Parker et al. (2001)	↑ Ehret et al. (1993)
Infanticide	↓ McCarthy (1990)		↓ Ogawa et al. (1998a)
<i>Sexual behavior</i>			
Female sexual behavior	↑ Albers and Bamshad (1998), Arletti et al. (1992), Gorzalka and Lester (1987) and Caldwell et al. (1986)		↑ Rissman et al. (1999) and Ogawa et al. (1998a)
Male sexual behavior	↑ Witt (1997) and Arletti and Bertolini (1985)		↑ Rissman et al. (1999), Wersinger et al. (1997) and Wood (1996)

is that an estrogen response element occurs on both OT and AVP genes (Shapiro et al., 2000; Bale and Dorsa, 1997). These results further suggest that E regulates the expression and function of both oxytocinergic and vasopressinergic neurons.

5. Social behavior and the BST and MeA

Based on extensive overlap in function and interconnections between nuclei in the limbic system (BST, MeA, MPOA, lateral septum (LS), VMH, central amygdala, anterior hypothalamus), it has been proposed that these nuclei together form a network that regulates social behavior (Newman, 1999). While the regulation of social behavior is complex and involves a number of regions of the brain, two regions of the brain that may be particularly responsive to the effects of early social experience are the BST and the MeA. These two areas receive direct input from the accessory olfactory bulb and there is bi-directional communication between the two areas (the BST is classified by some as part of the extended amygdala). Not surprisingly, the BST and MeA are two of the first regions that show neuronal activation during social contact (Curtis and Wang, 2003; Cushing et al., 2003b; Swann et al., 2001;

Pfaus and Heeb, 1997; Kirkpatrick et al., 1994). The BST and MeA play a role in regulating mating behavior (Meisel and Sachs, 1994; Yahr et al., 1994) and a number of social behaviors. The BST and MeA play a significant role in the expression of social preferences, affiliation, and aggression in rats, mice, and hamsters (Ferguson et al., 2001; Newman, 1999; Rasia-Filho et al., 2000) and prairie voles (De Vries and Villalba, 1997; Wang et al., 1997; Wang and De Vries, 1993), suggesting these regions of the brain have a similar function in both highly social and less social species. In addition to having projections to the MPOA and LS, the BST and MeA also project to the OT and AVP neurons of the PVN and SON (Sawchenko and Swanson, 1983), suggesting that both also can regulate the production or release of OT and AVP.

Several lines of evidence suggest a role for ER α in BST and MeA in regulating social behavior. First, Kansas and Illinois voles, which differ in social behavior, have significantly different patterns of ER α expression in the BST and MeA (Cushing et al. (2004); Fig. 1). Second, manipulations early in life that alter social behaviors such as parental care and affiliation alter the expression of ER α in these areas (Champagne et al., 2003). Neonatal castration of prairie voles decreases male parental care (Lonstein et al., 2002), while increasing ER α in the BST and MeA (Cushing

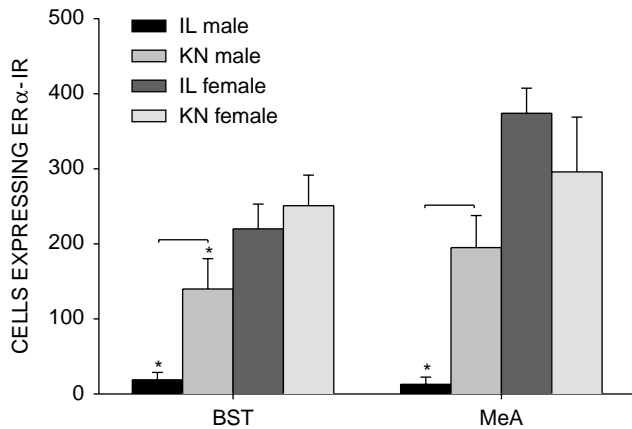


Fig. 1. Expression of ER α in the brains of adult male and female Illinois (IL) and Kansas (KN) prairie voles. There are significant differences between males and females and between populations in the number of cells expressing ER α -IR. Illinois males expressed significantly less ER α -IR than Illinois females in both the bed nucleus of the stria terminalis (BST) and medial amygdala (MeA), while Kansas males expressed less ER α -IR than Kansas females in the BST. Illinois males expressed significantly less ER α -IR in the BST and MeA than did Kansas males (adapted from Yamamoto et al. (in press)). —: significant difference between population, within sex ($P < 0.05$); *significant between males and females, within population ($P < 0.05$).

and Kramer (2005); Fig. 2). Neonatal manipulations of OT in prairie voles, which result in subsequent changes in affiliation and parental care, altered the expression of ER α in the BST and the MeA, as well as in the VMH and MPOA (Yamamoto et al., in press). This further supports a link between neuropeptides and estrogen in regulating the ultimate expression of social behavior. It has been hypothesized that it is a lack of ER α in these regions that increases the expression of prosocial behavior in male prairie voles (Cushing et al., 2004). This contention is

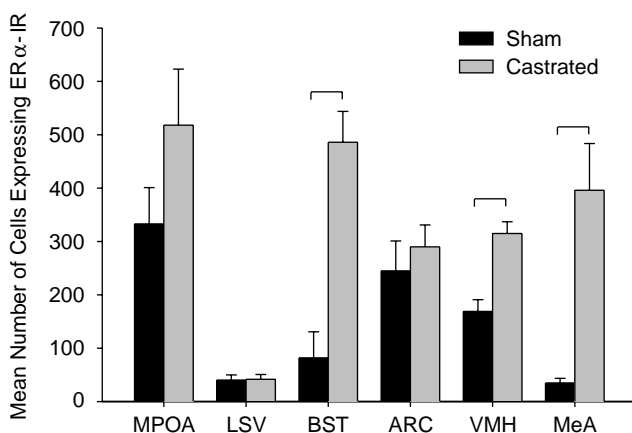


Fig. 2. Mean number of cells expressing ER α -IR by treatment. Neonatal castration significantly increased ER α -IR (examined in adults) in the bed nucleus of the stria terminalis (BST), medial amygdala (MeA), and ventromedial nucleus of the hypothalamus (VMH) compared with neonatally sham-castrated males. Increased ER α -IR was site-specific as there was no treatment effect in the ventral portion of the lateral septum (LSV), arcuate (ARC) or medial preoptic area (MPOA). —: significant difference between treatments ($P < 0.05$).

supported by the fact that male rats do *not* show a sexually dimorphic pattern of ER α expression in the BST and MeA while prairie voles do, suggesting that these differences could be important in regulating male social behavior.

The potential importance of the BST and the MeA is further indicated by the fact that they are part of the oxytocinergic and vasopressinergic systems. The MeA and the BST both contain neurons that possess OTR and V_{1a}R (Gimpl and Fahrenholz, 2001; Insel et al., 1994), and are sites of production of AVP (Bester-Meredith and Marler, 2001; Wang and De Vries, 1993). There is evidence of a direct link between the expression of social behavior and the action of OT or AVP in the BST and MeA. OT and AVP acting in either the BST or the MeA regulate aspects of social behavior. Infusion of OT into the MeA of OT knockout mice stimulated the formation of social recognition and memory (Ferguson et al., 2001). Monogamous California mice (*Peromyscus californicus*) cross-fostered to polygynous white-footed mice (*P. leucopus*) showed alterations in social behavior and corresponding changes in AVP production in the BST. These findings provide additional support for predicting changes in the BST and MeA in response to early social experience.

6. Potential mechanisms: Neuropeptide regulation during development

While there are relatively few studies which identify the mechanism by which social interactions affect brain development, in the following section we will address some of the potential mechanisms through which early social experience could affect neuropeptide production. Changes in neuropeptide production may, in turn, alter development of the brain. We focus on neuropeptides because their release and production are linked with physical contact and social interaction, including nursing, which are primary aspects of early mammalian social experience (Insel and Young, 2001). Changes in the oxytocinergic system, in response to social interaction, can alter the development of the brain and, therefore, subsequent expression of social behavior.

6.1. Oxytocin and the neonatal regulation of steroidal responses

Steroids play a major role in sexual differentiation and the expression of social behavior of both males and females. Therefore, regulation of steroidal effects during neonatal development may play a critical role in the subsequent expression of social behavior. As previously discussed (see above), the traditional view of the interaction of steroids and OT and AVP is that steroids regulate the oxytocinergic and vasopressinergic systems. There is, however, increasing evidence that under certain conditions OT affects the response to steroids. Neonatal manipulation of OT can

have long lasting effects on the expression of behavioral and physiological responses regulated by E. In female rats neonatal manipulation of OT delayed the onset of vaginal opening and first estrus (Withuhn et al., 2003), while in female prairie voles manipulation of OT on the day of birth affected sexual receptivity and increased the probability of successfully producing a litter in the absence of a mate (Cushing et al., 2005). These changes in steroid-regulated behaviors may result from changes in the expression of ER α , as neonatal treatment with OT increased the expression of ER α in prairie voles (Yamamoto et al., *in press*) and rats (unpublished data).

Although there are limited data at this point, there are several potential mechanisms of action of OT on the expression of ER α . In MCF7 breast cancer cell lines treatment with OT inhibited the ability of E to stimulate mitosis (Cassoni et al., 1997). The changes in response to E appear to be regulated by the ability of OT treatment to alter the production of ER α mRNA, binding affinity, and ER α transcriptional activity (Cassoni et al., 2002), suggesting that neonatal treatment with OT can alter the expression of ER α by directly altering the occurrence of ER α . It should be noted that while both studies of the effect of OT on cancer cells and in the brains of neonatally-treated voles and rats indicate that OT influences the expression of ER α , the direction of the effect is different. There are a number of differences between these studies including method of delivery in vivo vs. in vitro, doses, cell type, and species of cell origin. Any of these differences could have been a factor, i.e. neurons may respond differently from peripheral tissue. Further tests are needed to explain why the direction of OT effects differ.

In addition to affecting the production of ER α , OT could also influence the subsequent expression of social behavior by affecting cell survival, either of cells that express ER α or other cell types. During neonatal development OT affects cellular apoptosis in the developing ovary (Marzona et al., 2003). While these results do not relate directly to neurons, the location and timing of the effect are particularly relevant. Ovarian tissue contains large numbers of ER α , is the major site of E production in females, and the effect of OT occurs during development. E is known to be neuroprotective, reducing apoptosis (Behl, 2002; Bisagno et al., 2003; Harms et al., 2001; Kajta and Beyer, 2003; Wise, 2002). This means that the action of OT could represent multiple modes to affect cells survival/death. OT could directly affect cell death or indirectly by increasing or decreasing the expression of ER α , which could in turn affect the probability of neuronal survival. Changes in sensitivity to E by increasing ER α could then have additional ramifications on development as E may regulate the expression of brain-derived neurotrophic factor (Liu et al., 2001). In addition to suggesting possible mechanisms that could directly affect the brain, changes in the ovaries themselves could impact the development and timing of the expression of social behavior. If the increase in apoptosis is

in cells involved in the production of E this decrease plasma E, which could explain the delay in the onset of estrus and vaginal opening in female rats treated neonatally with OT (Withuhn et al., 2003).

One question that needs to be addressed is why OT may affect responses/sensitivity to E during the neonatal period, while having little or no effect in adults? First, the neonatal period is a time of significant development in the brain, compared with adults. Second, OTR are present in numerous regions of the neonatal brain and even occur in a number of regions which do not express OTR in adulthood, such as the cingulate cortex and the medial mammillary nucleus (Gimpl and Fahrenholz, 2001). Therefore, OT may be able to influence in regions of the brain that would be unaffected in adults due to a lack of receptors.

6.2. Oxytocin and the regulation of neuropeptides

As previously discussed neonatal manipulation of OT can directly affect OT production and may also alter OTR and V_{1a}R. Neonatal manipulation of OT in prairie voles increased the number of cells in PVN of neonatal females. The prairie vole PVN is not subdivided into discrete magnocellular or parvocellular regions (Yamamoto et al., 2004) and therefore at this point it is unknown whether changes are associated with changes in OT production/release peripherally, centrally, or both. While not directly linked, social behavior stimulates the release of OT and rat pups that receive care from high licking and grooming females increase the expression of OTR in females and V_{1a}R in males (Bester-Meredith and Marler, 2001). Taken together these findings suggest that OT could upregulate the expression of receptors and thus alter the expression of social behavior. Therefore, changes in the oxytocinergic system in response to early social experience may alter the subsequent expression of social behavior by affecting the development of responses to both neuropeptides and steroids.

6.3. Gene expression

Currently, there are limited data on the mechanisms by which early social experience alters neuroendocrine systems, but presumably it involves changes in gene expression. Recent studies have indicated two processes that could be involved, methylation of promoter regions on specific genes and deacetylation of related histones (Weaver et al., 2004). Interestingly, Weaver et al. (2004) demonstrated not only that early social experience is correlated with a change in methylation status, but that tissue-specific variants of the promoter region of the glucocorticoid receptor gene were altered. The result of such specificity is that methylation altered the expression of glucocorticoid receptors in a tissue-specific manner. Both methylation and deacetylation of histones appear to be involved in epigenetic changes in the expression of ER α (for review, see Pinzone et al. (2004)). These studies suggest exciting areas of

investigation that may shed significant light on how early social experience directly affects the development/organization of the brain.

7. Summary

This review has addressed the role of early social experience in the development and expression of social behavior through its effects on the function of the neuropeptides, OT and AVP, and steroids, with an emphasis on ER α . While genes are important regulators of social behavior, perhaps setting the boundaries of expression, the development and ultimate expression of social behavior can be strongly influenced by non-genomic/epigenetic factors. The postnatal period is a period of significant organization and development of the brain and in many animals, especially mammals, it is also a period of significant social interaction with parents and siblings. Therefore, early social experience has the potential to and has been shown to have a major impact on the subsequent development and expression of social behavior. It is clear that plasticity in the development of the CNS mediates changes in behavior that result from early social experience. While many social behaviors are the product of complex interactions and may include multiple brain regions and neuroendocrine systems, the interaction of OT and AVP with estrogen through ER α , has a major role in mediating the expression of social behavior. Although the mechanisms of the effect is still unknown, early social experience appears to be able to impact the organization of the oxytocinergic and vasopressinergic systems as well as patterns of ER α expression, thereby providing at least one explanation of the epigenetic regulation of social behavior. The importance of both steroids and neuropeptides in regulating social behavior should compel research to, whenever possible, study their interactions. As suggested by this review, this is a potentially rich area of study on how epigenetic factors such as early social experience can directly regulate social behavior.

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