Chapter 3

Behavioral Roles of Oxytocin and Vasopressin

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Additional information is available at the end of the chapter

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1. Introduction

Arginine Vasopressin (AVP) and oxytocin (OXT) are peptide hormones found in most mammals that have vital physiological and behavioral actions. The major sites of AVP production are the paraventricular (PVN) and supraoptic (SON) nuclei in the hypothalamus, although AVP and its receptors are found in numerous brain nuclei and peripheral tissues. AVP's physiological roles, which are mediated through both peripheral and central mechanisms, include regulating fluid homeostasis and blood pressure. It is also an important component of the endocrine stress response through its actions in the posterior pituitary gland, where it is a secretagogue of ACTH, stimulating the release of corticosteroid stress hormones and catecholamines from the adrenal glands. The three receptor subtypes for AVP are V1a, V1b, and V2. V2 receptors mediate the fluid regulating actions of AVP in the periphery, where the behavioral and central endocrine functions of AVP are mediated by the V1a and V1b receptors in the brain. These receptors are also involved in the central control of cardiovascular activity.

Oxytocin's major physiological roles are to facilitate uterine contractions during birth through a positive feedback mechanism during the second and third stages of labor, and to mediate milk letdown. In lactating mammalian mothers, OXT initiates milk letdown in the mammary glands, and the release of OXT is stimulated by suckling. OXT has one known receptor which has several alleles. The focus of the present chapter will be on the social behavior functions of both AVP and OXT. While some of these actions are mediated the PVN and SON, several other behaviorally active brain regions will also be discussed.

The behavioral roles of oxytocin and vasopressin have been studied and characterized in several animal species over the past few decades, and these findings have recently stimulated related work in humans. While the specific direction of the effects often vary between species, the general behavioral functions of AVP and OXT, as well as several related ancestral peptides, are conserved across taxa. The study of the diversity of these systems in birds [1] and fish [2] has been particularly useful in identifying the mechanisms

of the effects of these peptides on behavior. Although the behavioral roles of OXT and AVP are good examples of effective translation from animal models to clinical study for some topics, such as autism, there is still a need for increased communication and collaboration on many relevant issues, especially gender differences and stress related mood disorders. Both animal and human studies on depression and anxiety indicate that these neuropeptides have gender specific roles, and administering treatments developed in male animals and humans to females may be ineffective or have adverse consequences. The objectives of this review chapter are to present an updated summary of the gender specific behavioral roles of OXT and AVP in both animals and humans and stimulate translationally relevant gender specific studies on these hormones. The need for more female specific studies in this area is great, and this need will be underscored throughout the chapter. Behavioral topics covered include affiliation, aggression, parental behavior, depression/anxiety, and memory. Clinical topics discussed include depression, anxiety, addiction, and autism. Due to the broad scope of these objectives, this review chapter will highlight selected research and review papers on each topic, but will not be comprehensive.

2. Oxytocin in male animals

2.1. OXT and male animal affiliation

While most studies of both AVP and OXT conclude that OXT is a more important mediator of affiliative behavior in females than males, there is considerable evidence that OXT may serve important social behavior functions in males as well. The most convincing evidence for the role of OXT in affiliative behavior in animals is pair bonding in prairie voles (*Microtus ochrogaster*). These voles are relatively unique in their monogamous social structure, which is mediated by OXT and AVP activity in the brain. Central OXT infusions facilitate prairie vole pair bonding [3], which has been linked to gender specific developmental effects in male voles [4]. The distribution of OXT receptors in the brain mediates divergent social strategies in monogamous and polygamous vole species [5]. Studies of social recognition and memory in male mice, processes important for the establishment of affiliative behavior, conclude that OXT actions on social behavior are mediated by changes in recognition and social memory [6, 7]. In male rats, OXT facilitates sexual behavior through actions in the PVN [8]. In pair bonded tamarin monkeys, peripheral OXT levels vary with levels of affiliation and sexual behavior in both genders [9]. Specifically, OXT levels in male tamarins were correlated strongly with sexual behavior. In fish it has been postulated that isotocin (the teleostean homologue of OXT) is involved in courtship displays and territorial defense [10], and many of the social behavior effects of OXT are conserved across taxa [11].

2.2. OXT and male animal aggression

The recent data from stickleback fish suggest that the affiliative actions of OXT in vertebrates are associated with aggression [10]. OXT levels are highest in male sticklebacks that aggressively defend eggs and in subordinate males that fight to change their social status. Disruption of the OXT gene in male mice decreases aggression [12], yet OXT

knockout mice display elevated aggression which is postulated to be the result of decreased fearfulness [13]. One potential explanation for this inconsistency is indirect effects through AVP due to the neuroanatomical and biochemical similarities between the two neuropeptide systems. The increased aggression in OXT knockout mice may be mediated by a compensatory increase in AVP in these males.

2.3. OXT and animal paternal behavior

In polygamous male meadow voles (*Microtus pennsylvanicus*), paternal experience is associated with increases in OXT receptor binding in the accessory olfactory nucleus, bed nucleus of the stria terminalis, lateral septum, and lateral amygdala [14]. It was concluded that central OXT infusion increased the tolerance of the offspring by the father. Combined treatment with both an OXT antagonist and an AVP antagonist decrease male parental behavior in reproductively naïve male prairie voles, where treatments with only one antagonist did not affect the expression of alloparenting [15]. It appears that male prairie vole paternal behavior may rely on the neural effects of both peptides. Mandarin voles (*Lasiopodomys mandarinus)*, which are biparental and express parental behavior towards foster pups, increase central OXT expression following the development of male alloparental behavior. This increased expression may be mediated by elevated estrogen receptor alpha [16]. In support of this association between OXT and mammalian paternal expression, a recent primate study reported that icv OXT increased the transfer of food from fathers to their offspring [17]. Similar effects of OXT in male primates are supported by clinical data which will be discussed later in this review.

2.4. OXT and male animal models of depression and anxiety

Peripheral OXT has antidepressant effects in both young and old rats, and the effects in older rats are associated with enhanced memory [18, 19]. In the mouse tail suspension test, both systemic and central OXT decrease immobility time, which indicates that OXT decreased helplessness [20]. In contrast to these results, intracerebroventricular (icv) OXT did not affect behavior in the forced swim test of depressive like behavior in male rats selected for high or low anxiety, although it did have an anxiolytic effect [21]. Furthermore, isolated prairie vole males exhibit both anhedonia and increased plasma OXT following a resident intruder test of aggression [22]. As has been hypothesized for OXT elevation following maternal aggression, this increase could be due to the stress of the interaction, and may not be a causal factor for anhedonia. It is possible that anhedonia targeting tests of depressive behavior, such as saccharin preference or a naturally occurring reward mediated behavior (sexual behavior, maternal behavior), would reveal consistent anti-depressive actions of OXT.

2.5. OXT and male animal learning and memory

Most of the research on OXT and learning and memory has been limited to male models [23]. OXT mediates social recognition in several species [24], and male OXT knockout mice exhibit social amnesia [6], while other forms of memory are not affected. This effect on social

recognition is reversed by OXT treatment [7] and is mediated by the transmembrane protein CD38 [25]. A single dose of OXT can specifically impair memory retention [26], and further study indicates that exogenous OXT inhibits cholinergic mechanisms that are necessary for memory retention [27]. Another mechanism implicated in the amnesiac effects of OXT is glucocorticoid release, as dexamethasone is able to reverse the effects of OXT on memory [28]. While OXT may facilitate memory and social interactions in certain contexts such as pair bonds at certain levels, robust levels of OXT may impair social memory due to substantial glucocorticoid release or impaired cholinergic activity.

3. Oxytocin in female animals

3.1. OXT and female animal affiliation

OXT mediates the establishment and support of social bonds in several female mammalian species. Central injection of OXT specifically facilitates pair bonding in female prairie voles, similar to the role of AVP in males [3, 29, 30]. Studies of OXT receptor distributions in voles have identified expression patterns linked to species patterns of social organization, which support the manipulative studies [5, 11]. It has been postulated that the role of OXT in female rodent affiliation may be related to its effects on maternal behavior [31]. In primates, affiliation has been correlated with urinary OXT levels, including a relationship between the solicitation of sex and increased OXT levels [9].

3.2. OXT and female animal aggression

The data on the role OXT in female aggression are mixed, including several studies specifically on maternal aggression [32]. Although it was initially concluded that OXT in the PVN had excitatory effects on maternal aggression [33, 34], more recent studies involving OXT manipulations in the CeA and BNST conclude that OXT has inhibitory effects on maternal aggression [35]. Other studies reporting a positive association between OXT and female aggression postulate that OXT increases aggression by attenuating fear [34, 36, 37], but it is also possible that elevated OXT levels following maternal aggression are a result of the stress of the encounter [36]. In contrast, maternal separation decreases OXT immunoreactivity in lactating female mice, and this decrease was associated with an decreased latency to attack a novel male intruder [38], supporting earlier studies reporting an inhibitory effect of OXT on maternal aggression [39-41]. Several studies of the effects of cocaine on maternal aggression and oxytocin have also concluded that oxytocin has inhibitory effects on aggression [42-44]. In multiparous rats which are more aggressive than primiparous dams, OXT or OXT receptor levels are decreased in several behaviorally relevant brain regions compared to primiparous animals [45]. In general, the majority of the manipulative studies support the conclusion that OXT is inhibitory towards female aggression.

3.3. OXT and animal maternal behavior

The importance of OXT in the establishment of maternal care was initially reported in the late 70's and early 80's through icv injections of OXT [46, 47], which have been supported by

OXT antagonist administration [48-50]. OXT receptor knockout mice exhibit deficits in maternal care [51]. However, central OXT activity may not be a factor in all aspects of maternal care. The initiation of maternal care is impaired by the disruption of central OXT activity by lesions and antagonism of OXT [11], but since OXT disrupting lesions to the PVN of sheep do not disrupt maternal care once it has been established, OXT appears to be more important in the initiation of maternal care than the maintenance [52]. Other investigations in sheep have supported the hypothesis that OXT specifically mediates the induction of maternal care [53]. Comprehensive studies of natural variations in rodent maternal care indicate that OXT receptors mediate these differences, with high levels of OXT activity being associated with elevated levels of maternal care [54, 55]. These OXT actions are related to associated changes in dopamine activity [56] and both OXT receptor levels and maternal care are altered by exposure to gestational stress [57]. It is postulated that impairments in maternal care following gestational stress may be mediated by decreases in central OXT activity. The actions of OXT receptors in the nucleus accumbens have also been implicated in spontaneous maternal care in prairie voles [58]. OXT's role in maternal care induction parallels the importance of this peptide in parturition and lactation, and there is clinical interest in these parallels. Future animal work which includes the behavioral and physiological effects of OXT in maternal animals may identify treatments for disorders involving deficits in both maternal care and lactation.

3.4. OXT in female animal models of depression and anxiety

Despite the established role of OXT in maternal care, a potent reward mediated behavior; little effort has been directed at studying the role of OXT in female depression and anxiety. Much of the current focus on translational OXT work is centered on effects on social behavior, and related disorders such as seasonal affective disorder and autism. Central OXT decreases anxiety in pregnant and lactating rats, despite having no effect in virgins [59]. However, chronic icv OXT is anxiolytic in female rats selected for high levels of anxiety [21]. Studies using ovariectomized rats indicate that circulating estrogen is required for the anxiolytic effects of OXT, which is likely to involve dynamic estrogen dependent changes in OXT receptor levels [60]. This dependence on estrogen may explain the divergent results in maternal and nulliparous rats considering the robust hormonal changes of pregnancy and lactation [61]. Elevated plus maze (EPM) testing indicates that the anxiolytic effects of OXT may be most potent in stressful context, as OXT is only anxiolytic when the EPM is presented as a novel environment [62]. These data are relevant to the clinical observation that exposure to stress is a significant predictor of depression in females [63]. The animal literature on OXT and maternal care and the consistency between animal and human work make this neuropeptide a strong target for human studies of postpartum depression.

3.5. OXT and female animal learning and memory

The majority of the studies on OXT and memory in female animals investigate social recognition. The disruption of endogenous OXT activity impairs short-term olfactory memory in female rats [64], and mice with a conditional OXT knockout display impairments

in social recognition [65]. In sheep, a functioning OXT circuit in the olfactory bulb is required for offspring recognition [52]. These effects of OXT on offspring recognition are mediated by GABA, norepinephrine, and acetylcholine and are crucial to the role of OXT in maternal care induction [66]. It has also been postulated that the effects of OXT in pair bonding involve a social recognition function [67]. Similar to studies of the roles of dopamine and AVP in rodent maternal memory (the ability of a dam to quickly return to maternal care following a separation from her pups) [68, 69], central OXT is involved in the consolidation of maternal memory [70]. One hypothesis is that the effects of both OXT and AVP are mediated by their actions on dopamine. Although some studies of ongoing maternal care conclude that OXT is not necessary once offspring care has been established [11, 52, 71], these data on maternal memory indicate that its importance to maternal care may extend beyond the initial stages of maternal care.

4. Oxytocin in male humans

4.1. OXT and male human affiliation

The investigations of OXT and affiliation in humans do not necessarily examine affiliation directly. For instance, intranasal OXT promotes trust and prosocial behaviors which are critical to human bonding and it is also associated with trustworthiness [72, 73]. Intranasal OXT increases cooperation following unreciprocated cooperation in a social experiment and this behavioral effect was associated with increased fMRI activity in OXT regions associated with affiliation [74]. Studies investigating affiliation and/or sexual behavior conclude that the effects of OXT are often mediated by direct physical contact as increased plasma OXT has been recorded in men during social contact with a partner [75], and during orgasm [76-78].

Impaired affiliation has been associated with decreased plasma OXT in autistic patients [79]. Normal affiliative expression is especially impaired in autistic males, and some autistic males have deficits in OXT receptor expression [80, 81]. Several cases were associated with hypermethylation of the OXT receptor gene and a decrease in OXT receptor mRNA. Furthermore, clinical studies have reported enhanced social interactions (eye contact, social memory) in autistic patients following intranasal OXT [82]. Several labs have investigated the use of OXT for the treatment of social behavior deficits in autism [82-84] and social anxiety disorder [85], and research in this area is ongoing.

4.2. OXT and male human aggression

Compared to the interest in OXT and human prosocial behavior, there are few studies of the role of OXT on male aggression. The established effects on affiliation and prosocial behavior in animals and humans support the hypothesis that OXT has inhibitory effects on aggression. Conversely, some have postulated that OXT's anxiolytic effects could result in increased aggression, but there are no behavioral data in support of this theory. One potential clinical role of OXT is in the treatment of PTSD associated aggression.

4.3. OXT and human paternal behavior

There is some evidence that OXT mediates human paternal care as well as maternal care. Plasma and salivary OXT has been associated with paternal social engagement, affect synchrony, and positive communication sequences, and fathers who exhibit high levels of stimulatory contact with 4-6 month old infants have elevated OXT levels compared to fathers that do not exhibit high levels of contact [86]. Intranasal OXT increases the responsiveness of fathers during play with their children, and may decrease hostility, which supports a causal role for OXT and positive paternal behavior [87]. The decrease in hostility offers indirect support for an inhibitory effect on male aggression. Finally, both maternal and paternal plasma OXT levels predict coordination of behaviors between parents and their children, indicating that OXT may have a positive effect on family interactions [88, 89]. Collectively, these recent studies indicate that OXT modulates several forms of family associated social behavior.

4.4. OXT and male human depression and anxiety

The interest in OXT as a potential treatment for mood disorders is based on the animal literature supporting the involvement of OXT in reward mediated and social behaviors [90, 91], which are often impaired in depressed individuals. Reduced plasma OXT has been observed in humans suffering from depression [92, 93], and detailed investigations of depressive symptoms indicate that high levels of plasma OXT are associated with a decrease in the severity of symptoms [94]. However, some studies have been unable to find depression related differences in plasma OXT [95]. Since OXT has both central behavioral effects and peripheral physiological effects, the exact functions of elevated plasma OXT are not clear. The few studies which have measured OXT activity in postmortem samples of depressed patients have reported increases in depression associated OXT immunoreactivity [96] and OXT mRNA in the PVN [97]. The increase in OXT mRNA in melancholic patients compared to non-melancholic depressives suggests that changes in OXT are specific to the type of depression. With anxiety, intranasal OXT has minor effects in male patients with seasonal affective disorder [85]. Given the strength of the animal work on the prosocial and reward mediated actions of OXT, it is surprising that there is not more interest in this target for treating depression and/or anxiety.

4.5. OXT and male human learning and memory

Intranasal OXT facilitates socially reinforced learning and emotional empathy in men [98], consistent with the data from animal models and the initial studies of the effects of OXT in autistic patients. Another study reported that OXT's effects were specific to the social stimuli of facial expressions, and did not affect financial associations in an associative learning task [99]. The available evidence supports the conclusion that OXT facilitates social reinforced learning and memory in human males, and these effects may be mediated at the amygdala [98].

5. Oxytocin in female humans

5.1. OXT and female human affiliation

OXT levels in females rise during massage, genital stimulation, copulation, and orgasm [11, 100] which parallels the association between OXT and physical contact in men. In a study of intrapersonal couple conflict, intranasal OXT increases positive communication and decreases plasma cortisol [101]. It is suggested that OXT may facilitate pair bonding in humans, as in voles. Women with more supportive partners have increased OXT before, during, and after a 10 minute period of physical contact [75]. In contrast, OXT is positively correlated with interpersonal conflict [102, 103], but the relevance of these changes in OXT is debated [104]. This increase in OXT may be in response to the conflict and not a causal factor. Some have speculated that plasma OXT may be a reliable biomarker of distressed relationships in female humans [105]. Intranasal OXT alters the neural response to emotional faces in women, and these effects differ from the effects in males (Domes 2010). One hypothesis is that OXT increases as a mechanism to ameliorate the negative effect of the conflict on the social bond, but further manipulative studies are needed in this area.

5.2. OXT and human maternal behavior

OXT is an important mediator of maternal-infant bonding in humans [106]. Increasing OXT during pregnancy is associated with enhanced maternal bonding [107]. Maternal behaviors such as gazing at the infant, touching, and attachment related thoughts are associated with OXT levels in both early pregnancy and postpartum periods [108]. Mothers who display high levels of affectionate contact exhibit an increase in plasma and salivary OXT, while similar increases are not exhibited by mothers displaying low levels of contact [86]. The primary importance of OXT in human maternal behavior appears to be in enhancing bonding during the first few weeks of lactation [71, 109]. Furthermore, mothers viewing images of their own infants increase brain activity in reward nuclei that contain high levels of OXT and AVP receptors [110]. In breastfeeding women, basal OXT levels are negatively correlated with anxiety and guilt [111], and plasma OXT in mothers is also associated with affectionate touch between mothers, fathers, and offspring [88]. It is concluded that OXT is an important mediator of the formation and maintenance of the family unit. Mothers that may have less efficient OXT systems display lower levels of sensitive responsiveness to their 2 year old toddlers [112]. Intranasal OXT treated mothers use less handgrip force in response to infant cry sounds, but this effect is only present in mothers who were not harshly disciplined as children [113]. One explanation for these effects is that high levels of early life discipline have developmental effects on central OXT circuits which make these individuals less responsive to exogenous OXT. In mothers who used cocaine during pregnancy, decreased OXT levels were associated with greater hostility and depressed mood, results consistent with animal studies reporting inhibitory effects of OXT on aggression. These mothers were also less likely to hold their babies, suggesting impaired bonding [114]. In a fMRI study, securely attached mothers exhibited a more robust OXT response to images of their own infants when crying and smiling, and also had increased

neural responses in brain regions association with reward, such as the ventral striatum [115]. Most notably, it has recently been reported that low plasma OXT concentrations during pregnancy are associated with an increased risk for postpartum depression. Plasma OXT concentrations in mid pregnancy significantly predicted PPD symptoms at 2 weeks postpartum [116]. Taken together, the data on OXT and maternal behavior strongly support the targeting of central OXT in the development of new treatments for maternal mood disorders.

5.3. OXT and female human depression and anxiety

Although plasma OXT is difficult to measure and has a high degree of variability, reduced plasma OXT has been documented in both males and females suffering from depression [117]. Changes in the variability of OXT pulses have also been reported in women with major depression [118]. Given the gender differences reported for the roles of AVP and OXT in animal studies, it is likely that there are neuroendocrine differences in the role of OXT and AVP in human depression as well. Studies of maternal humans suggest that OXT may be specifically involved in the development of postpartum mood disorders. Women with lower plasma OXT while interacting with their own infants are at an increased risk for depression due to low attachment ratings as adults and low attachment ratings for their children [115]. Cocaine addicted mothers, who are at an increased risk for postpartum mood disorders which result in impaired maternal infant attachment also have depressed plasma OXT levels [114]. Childhood trauma, which is a reliable predictor of adult depression, has been associated with decreased CSF OXT and high levels of anxiety [119, 120]. Both prior stressful events and current exposure to stress are significant predictors of postpartum depression, so the association between stress and OXT may be involved in a common mechanism for the development of postpartum mood disorders. As mentioned previously, low plasma OXT during pregnancy predicts an increased risk for postpartum depression [116] and elevated OXT in postpartum women is associated with low levels of anxiety [111]. The advantage of targeting clinical studies of OXT and depression at postpartum depression is that improvements in these patients is also beneficial to the rest of the family, and may represent a preventative target for the offspring of depressed mothers. Furthermore, there has been recent speculation that failed lactation and perinatal depression have related neuroendocrine mechanisms [121]. Failed lactation is common in depressed mothers, and in many cases can exacerbate symptoms of depression in mothers.

5.4. OXT and female human learning and memory

The strongest support for a role of OXT in human memory is found in studies of affiliation. Social bonds require memory related components of social recognition. It is postulated that OXT's role in bonding involves social recognition and memory mechanisms [122]. Studies from male subjects suggest that despite a potential amnesiac function of OXT in certain paradigms, central OXT may enhance social memory [123]. It is unknown whether OXT has similar effects in women.

6. AVP in male animals

6.1. AVP and male animal affiliation

There is a wealth of studies of AVP and affiliation in voles [11]. Central administration of AVP to monogamous prairie voles that live in burrows with extended families induces several forms of bonding behaviors [124, 125], and AVP V1a receptor antagonist treatment blocks pair bonding behaviors in males [124, 125]. In polygamous montane voles (*Microtus montanus*) that live in solitary burrows, AVP or V1a antagonist treatments have no effects on social behavior. These behavioral differences are reflected in the neural OXT and AVP maps of these species [5]. Over-expression of V1a receptors in the forebrain of male prairie voles enhances pair bonding [126], and V1a antagonist injection into specific brain regions inhibit pair bond formation [127, 128]. The pattern of AVP mediated pair bonding in males and OXT mediated pair bonding in females has been identified in several other species [129]. Although there is no clear picture of how AVP expression patterns relate to social structure, AVP is an important mediator of affiliation in many vertebrate species, including fish [2] and birds [1]. The variety of social structures and central AVP circuitry among vertebrate species presents a valuable opportunity for both descriptive and manipulative comparative studies.

6.2. AVP and male animal aggression

Initial studies in male hamsters reported that V1a antagonist administration into the anterior hypothalamus inhibits aggression [130, 131], results which have since been confirmed in several other labs [132-134]. Exogenous AVP in the anterior hypothalamus can stimulate offensive aggression [133, 135], but this effect may be modulated by social environment [136]. Further work in hamsters has revealed that an orally active V1a antagonist decreases aggression in male hamsters, but does not affect social investigation or sexual motivation [137]. Anabolic steroid treatment of adolescent males increases aggression which can be inhibited by V1a antagonist treatment in the AH [138], indicating that the elevated aggression is mediated by central AVP activity. A similar effect of amphetamine has been documented in male prairie voles, where increased aggression is associated with increased V1a receptor binding in the AH [134]. Developmental effects of AVP have been reported in male prairie voles, where early postnatal peripheral injections of AVP increase adult aggression [139]. However, maternal separation in mice increases AVP in the paraventricular nucleus and decreases intermale aggression [38]. This effect is similar to much of the behavioral data from female animals, which indicate that AVP has suppressive effects on maternal aggression and intraspecies aggression.

6.3. AVP and animal paternal behavior

Research on AVP and offspring care by males includes studies in several rodent species. The increase in paternal behavior in cohabitating meadow voles is mediated by AVP, as treatment with AVP antagonist decreases paternal behavior [14, 140]. Elevated AVP in meadow voles stimulates paternal behavior through both a decrease in pup directed

aggression and an increase in paternal behaviors [14]. Alloparental behavior in naïve male prairie voles also involves central AVP actions [15]. Monogamous male California mice are more paternal and aggressive towards nest intruders than polygamous male while footed mice, and these differences are associated with elevated AVP in the BNST and LS [141]. These paternal styles may be transmitted through behavioral effects, as cross-fostering paternal behavior is similar to the foster parent behavior [142]. Pup directed aggression may be decreased and paternal care increased through social bonding mediated changes in central AVP. It is likely that the effects of AVP on paternal behavior are related to its general role in social bonding.

6.4. AVP and male animal models of depression and anxiety

Anxiety related behavior on the elevated plus maze is decreased following septal AVP antagonist treatment or antisense treatment in male rats [143, 144]. In contrast, other studies report that intraseptal and intraperitoneal AVP is anxiolytic [145]. An anxiogenic role of AVP is supported by male AVP V1a receptor knockout mice which exhibit lower levels of anxiety compared to wild type [24, 146]. Once again, other investigations of this line have failed to find differences in anxiety [147]. The oral and intraperitoneal administration of an AVP V1b antagonist is anxiolytic in several tests of anxiety [148-150], but AVP V1b receptor knockout males may not exhibit decreased anxiety [147, 151]. The lack of differences in anxiety related behaviors in these knockout mice may be due to compensatory mechanisms during development. In male rats bred for high levels of anxiety, AVP level and release from the PVN are elevated when compared to low anxiety males [152-154] and the differential expression of AVP in rats selected for high anxiety has been linked to specific single nucleotide polymorphisms [155, 156]. Central AVP V1a receptor antagonist treatment decreases anxiety and depression associated behaviors in high anxiety males [154]. The forced swim test induces both depression associated behavior and elevated AVP in the SON and PVN [157, 158]. V1a antagonist treatment to both the mediolateral septum and amygdala has antidepressant like effects in male animals [159, 160], and similar effects are documented following V1b receptor antagonist treatment [148, 161]. For male animals, there is evidence to support the hypothesis that depression and anxiety related behaviors are associated with elevated AVP activity in both brain and plasma.

6.5. AVP and male animal learning and memory

Infusion of AVP into the lateral septum of wild type and AVP deficient Brattleboro rats enhances social memory, and these effects are impaired by antagonist or antisense treatments [162, 163]. The over expression of vole V1a receptors in rats enhances social discrimination abilities [164]. However, studies of V1a and V1b KO mice have had mixed results, with some reporting impaired social recognition [24, 151] and others failing to find impairments [165]. AVP has also been implicated in both memory consolidation [166] and memory retrieval [167, 168]. The social aspects of AVP's effect on memory suggest the roles of this nonapeptide in memory and affiliation are related.

7. AVP in female animals

7.1. AVP and female animal affiliation

Most of the work on AVP and pairbonding in voles has focused on the male vole. Several studies indicate that OXT is more important than AVP for female pair bonding [169]. It is known that OXT receptor and AVP V1a antagonists prevent pair bond formation in both males and females [170]. Studies of AVP and maternal behavior indirectly support the hypothesis that AVP is a mediator of female affiliation [48, 171], but it is unknown if these effects pertain to adult conspecific affiliation. Additional studies on females are needed to determine if central AVP also is a significant mediator of the female component of pairbonding.

7.2. AVP and female animal aggression

Several studies have reported that AVP has inhibitory effects on maternal aggression towards a male intruder, which contrasts with the stimulatory role of AVP in male rodent aggression. V1a antagonist treatment increases maternal aggression in both primiparous and multiparous dams, and AVP injection decreases maternal aggression in highly aggressive multiparous rats [171, 172]. An inhibitory role for AVP in females is also supported by multiple experiments in non-maternal female hamsters [173]. Gene expression analysis of primiparous and multiparous rats indicates that changes in both AVP and OXT may be involved in the parity associated increase in maternal aggression in multiparous rats, as high levels of aggression are associated with low levels of AVP and OXT activity in several nuclei [45]. fMRI study of the neural effects of V1a antagonist treatment during the presentation of a novel male intruder reveal that this treatment may increase aggressive responding by enhancing the somatosensory responses to a male intruder and reducing fear responses in the cortical amygdala and ventromedial hypothalamus [174]. One hypothesis derived from these data is that AVP increases the perceived threat from the male intruder. Although some studies have found increased AVP release associated with maternal aggression, it is hypothesized that this release is triggered by the stressful nature of the encounter [36]. Manipulations of AVP in rat strains selected for anxiety behaviors reveal an excitatory function of AVP on aggression, but this effect on aggression only involves behavioral frequencies, and it is not known if the decreased frequencies are associated with increased durations of aggressive bouts [175].

7.3. AVP and animal maternal behavior

Recent studies indicate that OXT is not the only nonapeptide involved in the modulation of mammalian maternal care. Both AVP and V1a antagonist treatments decrease maternal care during exposure to a male intruder, with the effects of AVP associated with increased self grooming and the effects of V1a antagonist associated with elevated maternal aggression during resident intruder tests of maternal aggression [171]. Studies focusing specifically on maternal care conclude that central AVP promotes ongoing maternal care [48]. Furthermore, the blockade of V1a receptors around parturition impairs maternal memory, the ability of a

maternal dam to return to maternal care following a prolonged separation from her pups [68]. Although it has been postulated that maternal nurturing is linked to innate anxiety and OXT and AVP activity, this is based mostly on studies of rodent lines selected for anxiety [175]. Low anxiety mice display lower levels of maternal care compared to high anxiety mice, and acute icv injection of AVP increases maternal care and has anxiogenic effects [176]. These effects in mice were only moderately attenuated by cross fostering. An association between maternal care and innate anxiety was not supported in another study of maternal mice, although V1a receptors were correlated with pup grooming [177]. Animal studies suggest that AVP may be a worthwhile target for the development of treatments for anxiety associated disorders that affect maternal behavior, such as postpartum depression, which is often comorbid with anxiety.

7.4. AVP and female animal models of depression and anxiety

Many of the mechanistic studies of AVP and depression and anxiety have focused on males, and there is a need for more detailed studies in both nulliparous and pregnant and maternal females. As mentioned in the maternal behavior section, high anxiety rats and mice have elevated AVP activity in the PVN and display increased anxiety and depression behaviors [31, 176]. However, recent studies on a novel social stress mediated model for postpartum depression suggest that AVP can increase maternal care in animals subjected to the social stress paradigm that attenuates maternal care and aggression and impairs dam and pup growth during lactation [220]. At the present time, much of the available data on AVP and maternal behavior conflicts with the depression data from males, and treatments with V1a/V1b antagonists aimed at decreasing anxiety may have negative effects on maternal care.

7.5. AVP and female animal learning and memory

The little work that has focused on AVP and female memory has predominately used pregnant or maternal females. Female V1b knockout mice do not display the Bruce effect, where a previously mated female will block the implantation of fertilized eggs if exposed to an unfamiliar male after mating [178]. This suggests that the female's long-term social memory is impaired. As noted in the maternal behavior section, a V1a antagonist around parturition impairs the ability of a dam to re-initiate maternal care [68]. In general, the available data on AVP and female memory supports the literature from males concluding that AVP mediates various forms of memory consolidation and retention and has particular relevance to social memory. If the role of AVP in memory is substantial in human females, it is possible that depression and anxiety treatments targeted at antagonizing central AVP may impair memory processes.

8. AVP in male humans

8.1. AVP and male human affiliation

Intranasal AVP has been reported to enhance the encoding of emotional facial expressions in humans [179], as well as improving the recognition of sexual cues [180]. Other studies

indicate that intranasal AVP increases the negative emotional response to neutral facial expressions [181, 182]. These effects appear to be gender specific, as intranasal AVP in men stimulates agonistic responses to the faces of novel men, but stimulates affiliative facial responses in women and increases positive perceptions of these faces [181]. AVP increases cooperative behavior in men in response to a cooperative gesture in a social experiment, and this behavioral effect was associated with fMRI activity in brain regions involved in affiliative responses [74]. It has been suggested that plasma AVP may be a biomarker of distressed relationships in men [105]. Similar to several other behavioral topics, these gender specific effects need to be considered with respect to treatment development.

8.2. AVP and male human aggression

AVP levels in cerebrospinal fluid (csf) have been correlated with aggression in male humans [183]. However, a study comparing csf AVP in violent offenders vs. controls found no differences [184]. Patients with PTSD often have difficulties controlling their aggression levels, and clinical studies suggest that plasma levels are elevated in war veterans with PTSD [185]. Furthermore, intranasal AVP enhances physiological responding to combat images in male Vietnam veterans compared to saline and OXT [186], and AVP has been identified as a likely mediator for the effects of early life stress on the development of PTSD [187]. The available clinical evidence supports continued investigation of central AVP in the development of treatments for aggression disorders.

8.3. AVP and male human depression and anxiety

The first study suggesting that AVP was involved in mood disorders was from 1978 [188]. Plasma AVP is elevated in male patients with depression [95], and it has been suggested that increased AVP mRNA in the SON mediates the elevated plasma AVP levels [97]. Some have hypothesized that plasma AVP is specifically correlated to melancholic depression [97] as well as suicide [189, 190]. In terms of the prevalence of depression within a population, elevated plasma AVP is correlated with anxiety and a family history of depression [191, 192]. Resilience against depression has been associated with a SNP of the V1b receptor gene [193]. These data have generated continued interest in AVP antagonists in the treatment of mood disorders [194, 195].

8.4. AVP and male human learning and memory

Administration of an AVP analog enhances memory in human males [196, 197]. Treatment of boys with learning disorders with acute or chronic AVP increases the ability to remember stories. However, synthetic AVP may only affect reaction time, not memory [198]. In elderly humans, however, repeated intranasal AVP does not improve long term memory [199]. One hypothesis is that the memory enhancing effects of AVP are mediated by a general increase in arousal [200], although animal work suggests that AVP has specific effects on the molecular mechanisms of long term memory consolidation [201, 202].

9. AVP in female humans

9.1. AVP and female human affiliation

In contrast to the pro-aggressive effects of intranasal AVP in men, AVP induces affiliative facial motor patterns in women in response to the faces of unfamiliar women and increases the perception of the faces as friendly. This gender specific effect supports the animal work on AVP. In contrast, the AVP treatment increased anxiety in both sexes [181]. Homozygosity for the RS3 allele 334 doubles the risk of marital difficulties, and negatively influenced how the relationship was perceived by the spouse [203]. Central AVP activity may be a worthwhile target for gender specific treatments aimed at improving human pair bonds.

9.2. AVP and human maternal behavior

Studies of multiparous humans report that maternal sensitivity is associated with the AVP V1a receptor gene. Mothers with 2 copies of the long RS3 alleles were less sensitive than mothers with one or zero copies of the long allele, and this association was most prevalent in mothers exposed to high maternal adversity [204]. A valid question is how this polymorphism affects affiliation in females, as in the Walum et al. 2008 study. Exposure to maternal neglect is associated with depressed urinary AVP levels in children [205]. The effects were persistent despite being in a stable environment for three years following the maternal neglect. It was concluded that social deprivation inhibits the long-term development of the central AVP system, and this effect may be involved in the etiology of neglect associated mood disorders.

9.3. AVP and female human female depression and anxiety

Much of the research on this topic is focused on the interaction between stress, AVP, and depression. Specific V1b receptor haplotypes are associated with protection against recurrent major depression in both males and females [193]. A more recent study has found the association between V1b gene variants, AVP single nucleotide polymorphisms (SNP's), and vulnerability to childhood onset depression in females [206, 207]. In a study of male and female depression patients, plasma AVP was highly correlated with depression in non-treated patients, but this correlation was not found in patients taking anti-depressants [191]. These studies suggest that the central AVP system is a valid target for treatments for depression and anxiety.

10. Translation from animals to humans

10.1. Stress

There is a great deal of translational overlap in the research areas where focus on AVP and OXT is most relevant, and this is especially true with the studies on the effects of stress. Exposure to acute and/or chronic stress is often a predictor of depression/anxiety, addiction relapse, and relationship difficulties. It is suggested that the most valuable paradigms for

investigating the roles of AVP and OXT in depression, anxiety, or addiction involve exposure to chronic stress. The use of ethologically relevant stressors in animal models, such as social stress, is most likely to produce translationally consistent results (effects in animals which parallel clinical data). Many commonly used chronic stress protocols used in studies of AVP/OXT and depression and anxiety, such as chronic mild stress, do not use stressors associated with human disorders.

While the role of AVP in the endocrine stress response has been studied in detail at the animal level, the effects of stress on OXT are not as well known. Integrative investigations which include both AVP and OXT may indentify novel interactions between these behaviorally potent peptides. The most promising translational area may be PTSD. There is already evidence that male PTSD patients have high plasma AVP, aggression, depression and anxiety levels and similar behavioral effects have been associated with elevated AVP in animals. While it is difficult to separate the changes in depression and anxiety from impairments in social behavior, an increased focus on OXT in PTSD studies may provide insight on the social deficits in PTSD patients. Social bonds are often negatively impacted by exposure to chronic stress, and these bonds can have a positive buffering effect on the negative effects of chronic stress.

An indication of the potential value of social support can be seen in the cultural comparison of postpartum depression prevalence. Societies that have high levels of social support for mothers have low rates of depression, and cultures with low levels of support have much higher rates [208]. There is evidence that social support has protective effects in stress related mood disorders, and understanding the role of AVP and OXT in the positive effects of social support may help maximize the value of social support focused interventions.

10.2. Depression and anxiety

Increases the prevalence of stress related mood disorders [209] combined with metanalyses reporting that current treatments for depression may not be effective for mild to moderate depression [210] make a compelling argument that a new approach is needed in depression and anxiety research. Both the animal and human studies suggest that AVP is involved in the development of depression and anxiety disorders, and several reports indicate that AVP has gender specific roles. Continuing development of AVP targeted treatments should consider these gender specific actions. It is possible that while V1a antagonists may work for alleviating depression and/or anxiety symptoms in males, AVP or AVP agonists may be more effective in females. As noted by Manning et al. there has been little success with the development of non-peptide agonists and antagonists for AVP despite substantial investments by pharmaceutical companies. In contrast, some progress has been made with OXT peptide based treatments [194, 195]. The recent studies on AVP and maternal behavior in animals suggest that increased focus on AVP in human studies is warranted, especially on stress, maternal behavior, and postpartum depression. One valuable use for non-peptide ligands that have not been successful in clinical trials is as research tools, including the development of specific AVP and OXT ligands for imaging studies [194].

The animal and human data on OXT support the hypothesis that this peptide hormone is also a valid target for novel maternal mood disorder treatments. An interesting implication in this area is that synthetic OXT is already commonly used to induce labor, yet little is known about how this treatment may affect maternal behavior and/or offspring. OXT or OXT antagonists may also be effective in treating melancholic depression and seasonal affective disorder. There are also interesting non-pharmaceutical interventions which can manipulate OXT levels, such as physical touch and modified birthing practices and procedures (cesarean sections and induced labor vs. natural childbirth). Greater collaboration between animal and clinical researchers will accelerate the development of safe and effective AVP and OXT targeted treatments for depression and anxiety disorders, including postpartum depression, seasonal affective disorder, and PTSD. Projects that involve consistent interactions between animal and clinical researchers throughout the developmental process will be most effective. Another potential therapeutic application of AVP and OXT is in relationship counseling. Both of these hormones are likely to be involved in the mechanisms of establishing and maintaining the social bond necessary for a strong and stable relationship. AVP and OXT targeted treatments may be effective in treating the adverse effects of chronic social conflict, or the effects of other chronic stressors, especially in combination with behavioral cognitive therapy.

10.3. Addiction

Both affiliative behavior and addiction are mediated through similar central reward pathways. Central OXT pathways are also altered by addiction. Endogenous OXT activity is suppressed by chronic drug use, and elevated brain OXT levels may attenuate the negative effects of withdrawal [211]. There is preliminary evidence that exogenous OXT is capable of inhibiting stimulant and alcohol self administration and it may prevent stress and priming induced relapse [212]. As with autism, OXT centered treatments may be a useful adjunct to behavioral cognitive techniques. For example, intranasal OXT may augment the positive effects of extinction training for addiction [213] and/or reduce rates of relapse.

Levels of AVP mRNA increase in the amygdala during early withdrawal from cocaine [214], and the blockade of V1b receptors can block reinstatement in rodents [215]. In a rodent model of ethanol dependence, a V1b antagonist decreases excessive levels of ethanol self administration [216]. There is further evidence that AVP secretion is attenuated in response to social stress in the sons of alcohol dependent fathers, but it is unclear how these results relate to the risk of developing an addiction [217]. While data from humans is lacking, the involvement of AVP in the etiology of stress related depression and anxiety suggests that this hormone may be implicated in the long term effects of addiction and the mechanisms mediating relapse. V1b antagonism may be a productive translational target for not only drug dependence, but addiction associated depression and anxiety as well.

10.4. Autism

While current translational efforts with OXT and autism acknowledge that the effectiveness of intranasal OXT treatments may only be relevant to social behavior deficits, the animal

studies of AVP/OXT on learning suggest that there may be additional benefits to focusing translational studies in this area. One animal research topic that may be of particular interest is the developmental role of AVP and OXT. Treatments which only affect social behavior in older children or adults may be effective with other impairments when administered at a younger age. Changes in the brains of autistic children have been observed in children as young as 6 months [218]. Another issue with the current clinical trials of intranasal oxytocin is the level of dosing. There is debate as to how much OXT crosses the blood brain barrier and has central effects. One hypothesis is that developmental AVP manipulation may be able to address the cognitive impairments of autism. While most of the clinical efforts in AVP/OXT and autism are centered on the development of pharmaceutical treatments, environmental changes may also be effective. It is possible that insults during gestation, such as chronic social stress, are affecting the normal development of AVP/OXT mediated cognitive and social pathways. Another potential benefit of an OXT focused therapy may be as an adjunct to behavioral therapies aimed at improving social skills. One of the limitations of the current OXT manipulations is the available administration methods. The prairie vole partner preference model is a valuable tool for the screening of novel OXT treatments and administration methods [219].

11. Conclusions

In summary, increased translation between the animal research and clinical studies in males and females on the social behavior roles of AVP and OXT has the potential to stimulate rapid progress in the development of effective treatments for stress related disorders, including PTSD, depression and anxiety, and addiction, as well as disorders which involve deficits in affiliation, such as autism. These treatments may involve pharmalogical interventions, modifications to current practices, social interventions, or a combination of approaches. Stress paradigms which are ethologically relevant to both animals and humans, such as social stress for studies of depression and addiction, may generate the most useful data. PTSD and postpartum depression are two disorders that may benefit greatly from AVP and OXT focused studies. Given the available literature on the substantial gender differences in the roles of AVP and OXT, continued research on these peptide hormones needs to include studies of both males and females.

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