Psychology Research and Behavior Management

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REVIEW

Sexual dimorphism of oxytocin and vasopressin in social cognition and behavior

This article was published in the following Dove Press journal:
Psychology Research and Behavior Management

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Abstract: The neuropeptides oxytocin (OT) and vasopressin (VP) are hormones that are known to mediate social behavior and cognition, but their influence may be sex-dependent. This paper aims to provide a comprehensive review of the sex-related influence of OT and VP on social cognition, focusing on partner preference and sexual orientation, trust and relevant behaviors, memory modulation, and emotion regulation. Most studies have suggested that OT facilitates familiar-partner preference in both sexes, with females being more significant, increased trust in others, especially for male, enhanced memory in either sex, and reduced anxious emotion in males. However, VP-regulated social cognition has been less studied. Other relevant studies have indicated that VP facilitated familiar-partner preference, improved memory, induced empathy formation, increased positive-emotion recognition, and induced anxiety without any sex difference. However, there was a male preponderance among studies, and results were often too complex to draw firm conclusions. Clarifying the interplay between OT/VP and sex hormones in the regulation of social cognition is necessary for further applications.

Keywords: oxytocin, vasopressin, sexual difference, social cognition, social behavior

Introduction

Oxytocin (OT) and vasopressin (VP) are nonpeptide hormones. They differ by two amino acids, the third and the eighth amino acids, which are isoleucine and leucine for VP, and phenylalanine and arginine for OT, respectively. However, they have major physiological differences when acting on the central nervous system (CNS) and peripheral tissue. In peripheral tissue, OT facilitates lactation and uterine contraction during the perinatal period,[1] while VP plays an antidiuretic role.[2] In the CNS, OT and VP shape sex-based social cognition depending on their concentration and the variable expression of receptors in different brain regions. Several aspects of sex-based social cognition have been explored, including partner preference, trust and relevant behaviors, memory modulation, and emotion regulation. Some have shown salient sex-based differences, while others have not. In regard to the different aspects of social cognition, OT and VP have variable effects. Both OT and VP are archaic and highly conserved peptides across placental mammals, and their homologues can even be found in invertebrates.[3]

This review first introduces the conception of social cognition, OT, VP, and their receptor systems, then summarizes the animal models, intervention methods of OT and VP, and interplay between OT, VP, and sex hormones in different studies, and finally focuses on the role of OT and VP in the regulation of social cognition.

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DovePress
http://doi.org/10.2147/PRBM.S192951

Concept of social cognition

Social cognition is the ability that people or social animal process, store, and apply information about conspecifics, other specifics, and social stimuli. Assessing social cognition is a key to clarifying social psychology. The major concerns of social cognition include the sensing, coding, integration, and memory of social stimuli, affective effects on information processing, and behavioral outcomes of cognitive processes.[4] While social cognition is usually influenced by one's cultural upbringing,[5] at an individual level social cognition is also closely related to neurobiological homeostasis. Changing this homeostasis may affect various aspects of cognitive performance. Anatomic injuries of brain tissue,[6] novel activation of neuronal circuits, and disruption of neurotransmitters can also influence cognition. It is well known that OT and VP are brain neuropeptides that modulate social cognition.

OT, VP, and their receptor systems

OT is produced by the magnocellular neurosecretory cells of the supraoptic nucleus (SON) and paraventricular nucleus (PVN) of the hypothalamus and stored in the posterior pituitary.[7] OT is released into blood as a hormone from the posterior pituitary. In the PVN, other neurons project to the spinal cord and other parts of the brain.[8] OT binds both peripherally and centrally to the OT receptors (OTRs). In the peripheral nervous system, OT promotes lactation and uterine contraction during parturition. In the CNS, OTRs are expressed throughout the brain.[9] Hypothalamic OT neurons project axons to other brain regions and deliver OT for specific brain activities.[10] OTRs are not expressed evenly across the whole brain and show distinct differences across species, populations, life stages, and sexes,[11–15] which contributes to distinct social behaviors.[16]

In addition to magnocellular neurosecretory cells of the PVN and SON, VP is also synthesized by parvocellular neurosecretory neurons of the PVN. VP produced by magnocellular neurosecretory cells is stored in the posterior pituitary and later released into blood, where it acts as an antidiuretic hormone. VP produced by parvocellular neurosecretory neurons of the PVN is transported finally to the anterior pituitary, and is involved in the hypothalamic–pituitary–adrenal axis. In addition, the bed nucleus of the stria terminalis (BNST) and the medial amygdala are extrahypothalamic sources of VP.[17] VP receptors are classified into three subtypes: V_{1a} receptors (V_{1a}Rs), V_{1b}Rs, and V_2Rs.[17] The majority of VP receptors in the brain are V_{1a}Rs, while the second-most common are V_{1b}Rs. However, V_2Rs are primarily expressed in the renal collecting ducts, and have scarce expression in the brain.[17] As such, VP regulates social cognition, mainly through V_{1a}R and V_{1b}R.

Animal models

The prairie vole (*Microtus ochrogaster*) is a socially monogamous rodent, and is the premier rodent model for pair bonding.[18] Monogamous relationships are expressed as pair bonding, and belong to the category of social cognition. Monogamous animals usually form and maintain partner preference, which is considered one index of pair bonding.[19] The mandarin vole is another monogamous rodent,[20] and is also chosen as a primary animal model for pair-bonding studies. This kind of pair bonding usually refers to a relationship between opposite-sex pairs. To study the effect of OT on same-sex partner preference, the meadow vole is the preferred choice. The meadow vole is socially promiscuous, and its gonadal hormones are less secreted during winter, which is appropriate for nonreproductive social behavior research. In a winter day–length laboratory, female meadow voles have smaller uteri than those in summer day–length environments. The females can form partner preference for either same- or opposite-sex cage mates.[21–23] Laboratory rats usually include the Wistar rat, Long–Evans rat, Sprague Dawley rat, biobreeding rat, Brattleboro rat, hairless rat, Lewis rat, Royal College of Surgeons rat, shaking rat Kawasaki, Zucker rat, and knockout rat. This review includes studies using Wistar and Sprague Dawley rats as animal models, since they are used in OT-related memory-modulation tests. Other included animal models that are less used in studies, such as marmosets and macaques, are also listed in Table 1(OT) and Table 2(VP).

Intervention methods of OT and VP

Methods of intervention covered by this review (see Tables 1 and 2) include intracranial injection (intracerebroventricular injection), intranasal spray, subcutaneous injection, and intraperitoneal injection for rodents and nasal administration for marmosets and humans. Of note, increased OT concentration in the CNS can also be observed after intranasal administration of OT.[24,25]

Interplay between OT/VP and sex hormones

Androgen and estrogen exist in both males and females. These CNS sex hormones indirectly modulate sexual

Table 1 Animal models and species, doses, routes, and effects of OT administration

Models and species	outes	Doses	Effects	Reference
Prairie voles ♂	ICV injection	Artificial CSF: 2 μL OTR antagonist: 5 ng (Gly-NH_2 *d*[CH_2]5-[D-Tyr_2,Thr_4]OVT)	Facilitatedopposite-sex partner preference	30
Mandarin voles ♂+♀	Subcutaneous injection	OT: 3 μg Placebo	Facilitated opposite-sex partner preference in females	20
Prairie voles ♀	Viral vector gene transfer to nucleus accumbens (NAcc) injection	Overexpressed OTR in NAcc	Facilitated opposite-sex partner preference in females	38
Long–Evans rats ♀	Left lateral ventricle OT injection	OT: 1 μg Placebo	familiar object preference	42
Prairie voles ♂+♀	Intranasal; 21-day continuous intervention	Low: 0.08 IU/kg Medium: 0.8 IU/kg High: 8 IU/kg	Low–medium dosage decreased same-sex partner preference in males; high dosage–treated males and all females unaffected	41
Prairie voles ♂+♀	ICV injection	OT: 100 ng VP: 100 ng	Facilitated opposite-sex partner preference in both sexes	50
Macaques ♂+♀	Intranasally	OT: 8–28 IU Placebo	Increased working memory in males, not in females	54
Rats ♂	PVN injection	OT: 0.01 nmol/0.5μL Saline: 0.5 μL	Reduced anxiety	70
Prairie voles ♂	ICV injection	OT antagonist: 5 ng CSF	Reduced aggression in males	47
Prairie voles ♀	Intra-PVN injection	OT: 10 ng or 100 ng; OTR antagonist: 10 ng or 100 ng (des-Gly-NH_2,*d*[CH_2]$_5$[$Tyr(Me)^2$,Thr_4]OVT)	Reduced stress	96
Wistar rats ♀	ICV injection	OT: 0.1 μg/5 μL Placebo: Ringer's solution 5 mL	Reduced anxiety and aggressive behavior	73
Male and female adults	Intranasal	OT: 24 IU Placebo	Regulated prosocial behaviors context-dependently	97
Male and female adults	Intranasal	OT: 24 IU Placebo	Reduced anxiety only in men and was ineffective in women	98
Male adults	Intranasal	OT: 24 IU Placebo	Increased happiness perception, didn't decreased anger perception	99
Male and femaleadults	Intranasal	OT: 24 IU Placebo	Reduced negative affect in men; increased anger in women	100
Male and female-patients with chronic depression	Intranasally	OT: 24 IU Placebo	Reduced anger, increased happiness in both sexes	101
Male adults	Intranasal	OT: 24 IU Placebo	Decreased aversion to angry faces	102
Male adults	Intranasal	OT: 24 IU Placebo	Increased happiness perception	103

Abbreviations: ICV, intracerebroventricular; OT, oxytocin; PVN, paraventricular nucleus.

Table 2 Animal models and species, routes, doses, and effects of VP administration

Models and species	Routes	Doses	Effect	Reference
Male adults	Intranasal	VP: 20 IU Placebo	Improved memory for both happy and angry information in men	104
Male adults	Intranasal	VP: 20 IU Placebo	Reduced recognition of negative emotion in men	105
Male adults	Intranasal	VP: 20 IU Saline	Increased activity in amygdala via V_1R	106
CD rats ♂+♀	Intraperitoneal injection	$V_{1b}R$ antagonist: 1–30 mg/kg, weighing 25–30 g (V_{1B}-30N)	Blockage of $V_{1b}R$ diminished anxiety-like behavior in male rodents	77
Male and female adults	DNA extraction and genotyping for $AVPR_{1a}$ RS3 microsatellite	—	$V_{1a}R$ gene related to cognitive empathy	74
Wistar rats ♀	Medial–posterior part of BNST infusion	$V_{1a}R$ antagonist: $d(CH_2)_5$ $Tyr(Me)_2AVP$ 100 ng/0.5 μL SS149415: 100 ng/0.5 μL	$V_{1a}R$ in PVN of lactating rats mediated anxiety-like behavior	75
Brattleboro rats ♂+♀	P deficiency	—	Deficits in spatial working memory performance	69
Wistar rats ♂	ICV injection	VP against: 25 nmol (Aβ25–35); VP:0.1、1、10nmol	Protected spatial learning and memory	68
Prairie voles ♂+♀	Subcutaneous injection	One of three doses of VP: 1, 5, or 10 mg Saline: 50 mL	Facilitated opposite-sex preference	44
Prairie voles ♂	ICV injection	V_{1a} antagonist: 5 pg to 500 ng (VPA, $d[CH_2]_5Tyr[Me]$) CSF	Wide range of $V_{1a}R$ antagonists failed to exhibit aggression	47
Meadow voles ♂	V iral vector $V_{1a}R$ gene transfer to the ventral forebrain	— $V_{1a}R$ overexpression	Facilitated opposite-sex partner preference	46
Prairie voles ♂	$V_{1a}R$ viral vector gene transfer into ventral pallidal area	—	Facilitated partner preference	49
Sprague Dawley rats ♂	A988315 or water administered orally	A988315: 20 or 60 mg/kg (selective $V_{1b}R$ antagonist) Water	VP positively associated with recognition memory	60

Abbreviations: ICV, intracerebroventricular; VP, vasopressin; PVN, paraventricular nucleus.

dimorphism in social cognition through influencing OT, VP, and their receptors through discrepant gene expression. For example, the estrogen and androgen metabolites 3β-diol upregulate OT gene expression in the PVN via ERβ.[26] Estrogen regulates OTR gene expression in the medial amygdala through ERα[27] and increases OT expression in PVN.[28] OT mediates social cognition in both male and female, but is more prominent in females. However, the expression of VP seems to be mainly dependent on androgen, which is more abundant in the brains of males than in females.[29] As a result, VP seems mainly to mediate social cognition in males.[29]

Sexually dimorphic influence of OT and VP on social cognition

Partner preference and sexual orientation

In monogamous animals, OT and VP are the only neuropeptides that have been found to mediate partner preference. The partner-preference performance regulated by OT and VP in monogamous animals reflects the mechanism of sexual orientation in humans and underlies the basis of fidelity. The effects of OT and VP on males and females are discussed separately herein (Figure 1). The previously mentioned monogamous rodents — prairie voles and mandarin

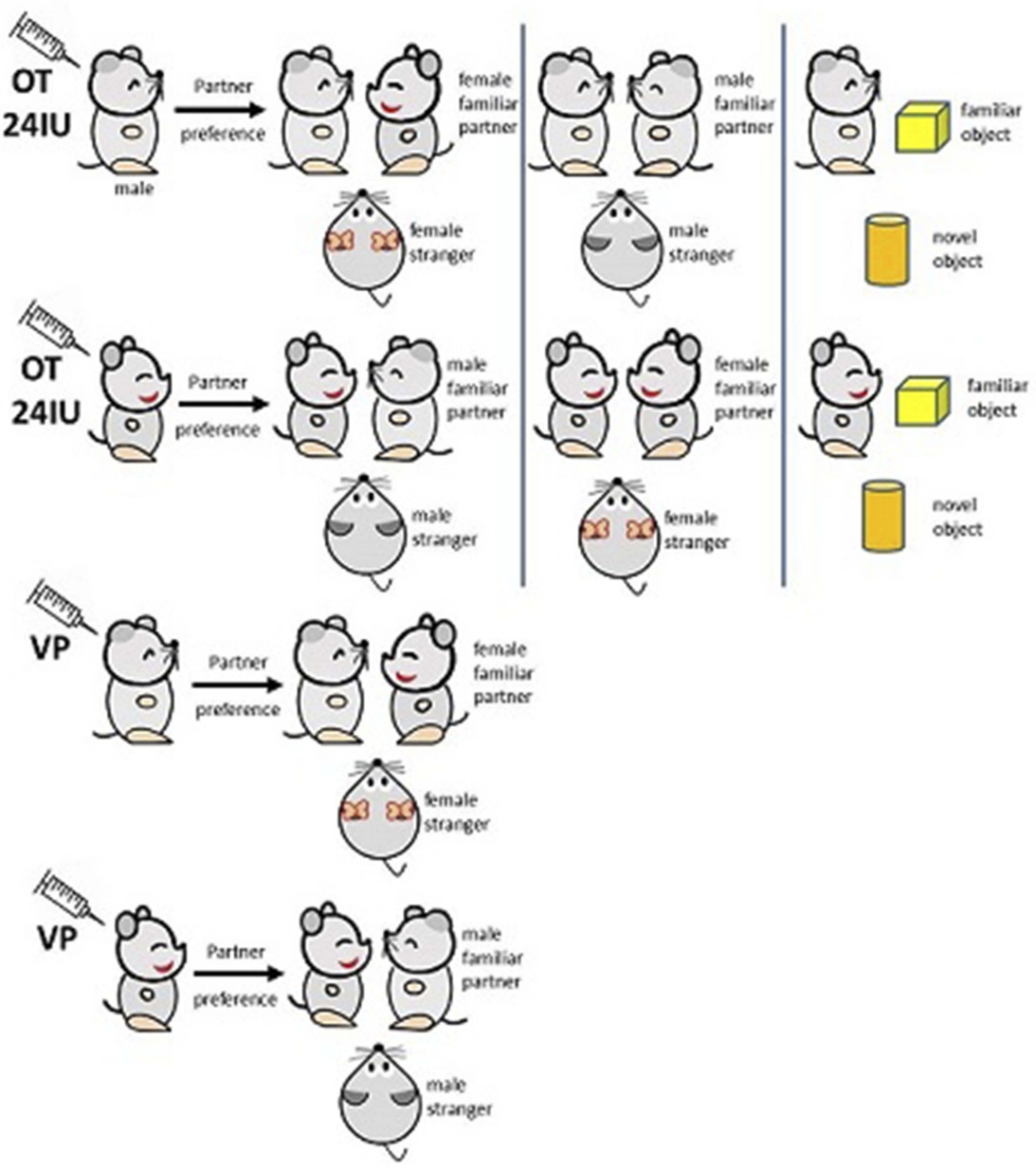

Figure 1 Influence of oxytocin (OT) and vasopressin (VP) on partner preference.

voles — and marmosets were used in the following studies. Animal models, intervention means, OT/VP dosage, and assessment methods in this field are listed in Tables 1 and 2.

Rodents or humans under temporary treatment with OT show a significant preference for familiar mates or objects in both sexes. This effect is not dependent on the intervention means and is more significant in females. Facing opposite-sex cage mates, prairie voles exhibit familiar-partner preference in both males[30–32] and females[19,33,34]with OT injections intracranially. Injecting the selective OTR antagonist *d*(CH)(Tyr[Me]Thr$_4$,Try-NHi into the left lateral ventricle blocks this effect.[19,34] Similar effects of OT can be found in male and female mandarin voles,[20] although this effect tended to be more prominent in females.[35,36] A study of prairie voles showed similar results in females, but not males, when OT was injected subcutaneously.[35] With marmosets as a model, intranasal OT resulted in females spending more time in close contact with partners and males spending less time with both partners and strangers.[37] The results were consistent with other methods to increase OT in the CNS substantially. For example, with viral vector gene transfer to overexpress OTRs in the nucleus accumbens of

female prairie voles during prepuberty, they showed accelerated partner-preference formation in adulthood.[38] When the choice was between two same-sex cage mates, both male and female voles chose the familiar partner,[39,40] but this was more critical for females. For instance, following a 21-day continuous intervention of low-dosage (0.08 IU/kg) and medium-dosage (0.8 IU/kg) OT, male prairie voles showed significant impairment of same-sex partner preference, while high dosage (8 IU/kg)–treated males and all females were unaffected.[41] This indicated that the familiar-partner preference is maybe dose dependent for males. Interestingly, for monogamous rodents, this effect not only occurred in conspecifics but was also seen in object preference. Centrally OT-treated female rats preferred a familiar object to a novel one.[42] According to these results, OT accelerates familiar-partner preference regardless of partner sex, although this was more obvious in females. The brain regions involvedare possibly different in females and males: nucleus accumbens in females,[31,38,43] and laterodorsal thalamic nucleus, lateral septum, posterior cingulate nucleus, ventroposterior thalamic nucleus,[44] and dorsomedial prefrontal cortex[45] in males.

VP enhances partner preference in both sexes (Figure 1), primarily by activating $V_{1a}R$ in the ventral pallidum.[46,47] Overexpression of $V_{1a}R$ in the ventral pallidum facilitates partner preference not only in monogamous male voles[48,49] but also in socially promiscuous male voles.[48] When using a $V_{1a}R$ antagonist or downregulating the activity of $V_{1a}R$, there is weakened partner preference in adult voles of either sex.[50–52] High-dose VP (80 IU) intervention through nasal mucosa for adult male monkeys led to frequent partner contact.[53] The partner-preference tests mentioned thus far were all performed between opposite-sex cage mates. As previously reported in other studies, VP appears to be more critical for male social cognition regulation.[36]

Both OT and VP are involved in the regulation of partner preference and facilitate the preference for familiar ones, although OT appears more important. More interestingly, this familiarity preference occurs not just between opposite-sex conspecifics but also between same-sex conspecifics and preference for objects. This phenomenon may be implicated in homosexuality. Future research into OT, VP, OTRs, and V_{1a} R gene-expression levels in postmortem homosexual brains may be useful.

Memory modulation

Animal and human studies on the relationship between OT/VP and memory have mainly been done in males, although several studies have included nonpregnant females. Females experience large hormonal fluctuations during the perinatal period, so studies on memory impairment in pregnant women are usually excluded.

OT has positive effects on social memory in either sex, but is more significant in males. Acute OT treatment increases working memory in male macaques, but not females,[54] and improves stress-induced memory impairment in both male and female Wistar rats.[55] Another study found that OT prevented stress-induced hippocampal memory and plasticity impairment in male Sprague Dawley rats.[56] Human studies have found that intranasal OT helps encoding and retrieval of recognition memory of negative social stimuli[57] and recall of social affiliation memories in men.[58] However, there have also been contrary results, eg, intranasally OT-treated men performed worse than a placebo group in visual object recall.[59] It should be noted that there is variable study design in this field, and future series-designed studies should aim to clarify the phenomena, functional/histological changes in the CNS and molecular mechanisms of how OT influences memory in either sex.

Studies have shown that VP improves memory, mainly via $V_{1a}R$.[60–63] VP acts on different brain areas, including the lateral septum[62] and hippocampus.[64] Other studies have shown that $VP_{4–9}$,[65] the main active metabolite of $VP_{1–9}$, and its derivative ($VP_{4–8}$),[66] have effects on memory modulation. Most studies have been performed only in males, and those that included both sexes did not find any significant sex difference. Memory evaluated in these studies included object-recognition memory,[60] social recognition memory,[67] short-term memory, long-term memory,[66] and spatial memory.[63,68,69] In general, studies found that men have better spatial sensibility than women, such as better direction-sense and geometric mathematical scores. This may well contribute to the spatial memory enhancement effect of VP. As previously mentioned, VP is more critical in males in the regulation of social cognition. To obtain more conclusive evidence, normatively designed experiments are needed in future.

Emotion regulation

OT and VP are also involved in the regulation of emotion, including anxiety, happiness, and anger (Figure 2).

OT reduces anxious emotion, which appears more prominent in males, although studies have used male rodents more frequently than females. CNS injection of OT into the hypothalamic PVN and periamygdala regions was found to decrease anxiety and amygdala activity in males.[70,71] When OT was infused into prelimbic region of the medial prefrontal

cortex intracerebroventricularly, anxious mood in females also remitted.[72,73] Of note, dosage of OT and treatment course modulated the study outcome. Chronic high-dose (10 ng/h for 15 days) intervention led to the development of an anxiogenic phenotype, while a low dose (1 ng/h for 19 days) prevented hyperanxiety in male mice.[71] The results of human studies using variable intervention methods are listed in Table 1. In general, high OT levels in the CNS are associated with lower anxiety in men, but not in women.

Studies of OT modulation of happiness and anger in humans are listed in detail in Table 1.

VP also appears to facilitate empathy formation, positive-emotion recognition, and anxiety (Figure 2) without any sex differences. It should be noted that $V_{1a}R$,[74,75] $V_{1b}R$,[76,77] and many other brain regions are involved in emotion regulation. Relevant studies and results are listed in Table 2.

In general, OT reduces anxious mood, which is more significant in males. OT also reduces perception of anger and increases perception of happiness in males, but facilitates the perception of anger in women. On the other hand, VP increases anxious feelings in both sexes, promotes the formation of empathy, and enhances the perception of positive emotions in either sex. However, its relationship with anger/happiness perception remains unclear (Figure 2). Men with high OT levels in the CNS appear more relaxed, insensitive, and optimistic, while pregnant women during their perinatal period seem to be more sensitive to others' emotions, especially anger. This change in women may be related to the sudden release of large amounts of intrapartum OT, and may be involved in the onset of postpartum depression.[78]

Implications for human studies

Human studies in this section explore how partner preference and trust are regulated by OT and VP. Human studies involve OT and VP being given by intranasal spray.

Partner preference

OT promotes human familiar-partner preference in ways analogous to monogamous rodents, although the preferred partner is not limited to the opposite sex.[79] After nasal administration of OT, men in a monogamous relationship preferred keeping a greater distance from an attractive female encounter,[80] while keeping a closer contact with a male friend.[45] To date, only one trial has been performed on homosexual men, where intranasal OT was associated with being easily attracted by men's faces, but not by facial expressions.[81] No study on homosexual women was found.

Trust and related behaviors

High OT levels in the CNS help to increase trust among people. Means of reflecting trust in these trials include the ultimatum game, dictator game, prisoner's dilemma, envelope task, and monetary game.

A study on the ultimatum and dictator games included only male adults. In the ultimatum game, the OT-treated decision-maker split more money to the other group member than controls. In the dictator game, the OT-treated decision-maker transferred less money to the other member compared to the ultimatum game, and no significant difference was found in comparison with controls.[82] OT may help to maintain an optimal balance between loss and

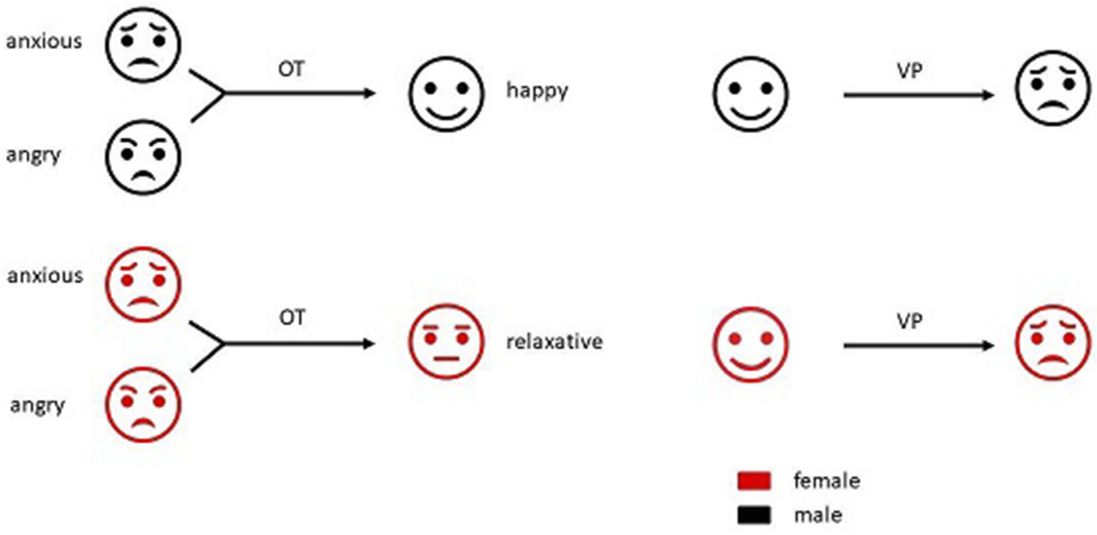

Figure 2 Influence of oxytocin (OT) and vasopressin (VP) on emotion in both sexes.

benefit. The decision-maker seemed to be more generous in the ultimatum game. OT appears to regulate trust-related behaviors in a context-dependent way. In the ultimatum game, the two members kept a gambling relationship, while in the dictator game the decision-maker owned full discretion. Differences between the ultimatum game and dictator game are displayed in Figure 3.

There have been several studies using the prisoner's dilemma, envelope task (Figure 4),[83] and monetary game (Figure 5)[84] to research trust-related behaviors. The study

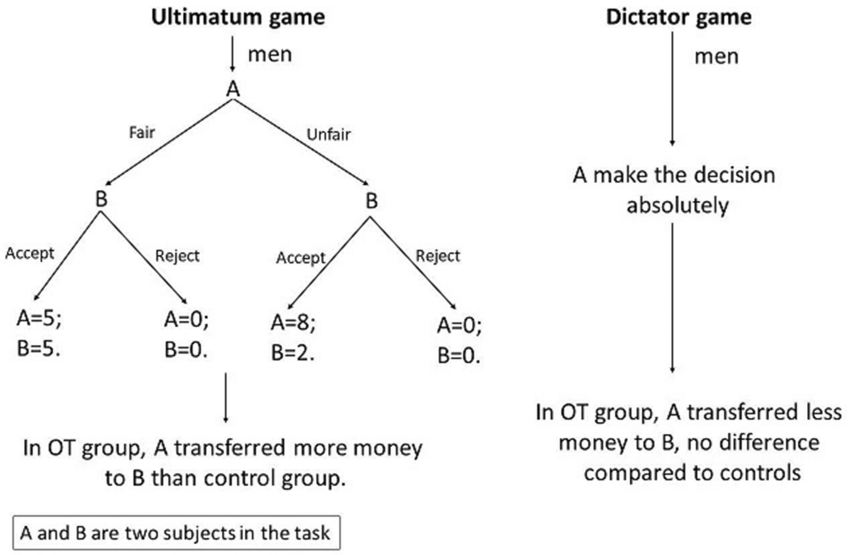

Figure 3 Ultimatum game and dictator game.
Notes: In the ultimatum game, A is endowed with $10 before the game starts. A may split $5 or $2 to B. B may accept or reject the money split from A. When B accepts, both A and B receive the corresponding amount of money. However, if B rejects, either A or B achieves no money. The dictator game is derived from the ultimatum game. A is the only decision-maker to determine the amount of money each person gets.
Abbreviation: OT, oxytocin.

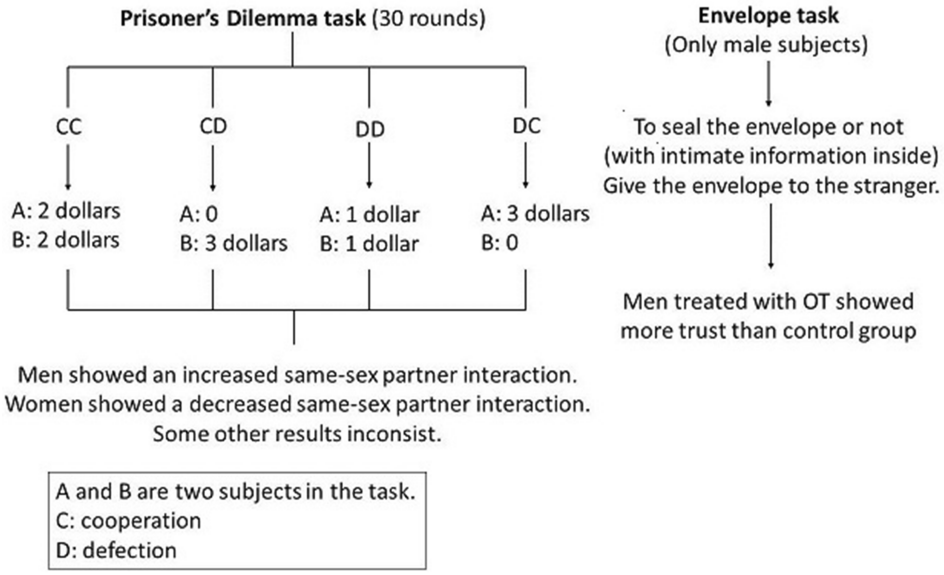

Figure 4 Prisoner's dilemma and envelope tasks.
Notes: In the prisoner's dilemma, A and B make sequential choices, which means A chooses to cooperate or defect first and then B is able to see A's choice before making her/his own choice. There are four outcomes in total, and each is associated with a different payoff. In the envelope task, participants place intimate information into an envelope anonymously and hand it to a stranger. All participants can choose to seal (even add sticky tape to) the envelope or not. Assessment criteria are the degree of openness of the envelopes, with totally open indicating utmost trust.
Abbreviation: OT, oxytocin.

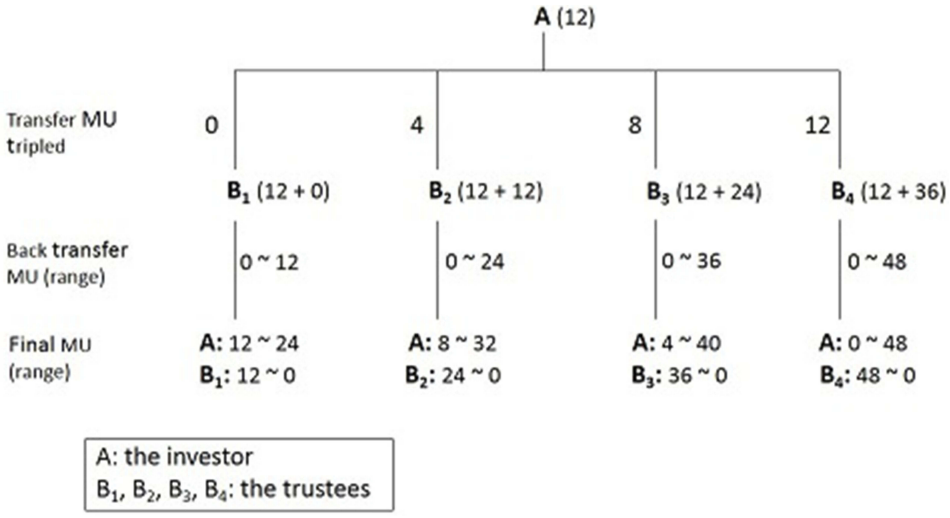

Figure 5 Monetary game.
Notes: There are two parts tothis game. Both A (the investor) and B (the trustee) are participants, and receive an initial endowment of 12 monetary units (MUs). In part one, A chooses to send 0, 4, 8, or 12 MUs to B (B_1–B_4, respectively). The MUs B receives from A are then tripled. In part two, B is free to send any amount of MUs between 0 and the total MUs available back to A.

designs and OT-detection means were similar, and validity criteria were controversial. Overall, OT contributes to increased feelings of trustworthiness in men. Few studies on women and on how VP influences trust-related behaviors have been done.

Discussion

The results of this review support the notion that OT can facilitate familiar-partner preference, increase trust, enhance memory, and reduce anxious emotion. There were sex differences on the effects of OT on partner preference, trust, memory, and anxious emotion, with the first more significant in females and the latter three more obvious in males. On the other hand, VP can facilitate familiar-partner preference, improve memory, induce empathy formation, increase positive-emotion recognition, and induce anxiety without any sex difference. In addition, as verified by many trials, OT regulates a series of social cognitions. However, there is significant heterogeneity across studies in terms of the type of animal model and behavioral paradigm used.

Centrally increased OT-facilitated partner-preference formation is achieved by increasing the contact time between OT-treated rodents and their same- or opposite-sex partner during cohabitation. Cntrally increased OT in neonatal rodents reduced Fos expression in the SON, PVN, lateral septal nucleus, medial preoptic area, BNST, ventromedial nucleus of the hypothalamus, mediodorsal thalamic nucleus, the central amygdaloid nucleus, and medial amygdaloid nucleus (MeA) in females, but decreased in the PVN, BNST, and mediodorsal thalamic nucleus and increased in the medial preoptic area, central amygdaloid nucleus, and lateral septal nucleus in males.[20] Fos in these studies was used as a marker of neural responses to social stimuli. These results indicated that neonatal manipulations of central OT changed neural activity of specific brain regions. OTRs mediated neural activity. Activation of OTRs in anteromedial BNST of female mice resulted in vigilance responses which promotes avoidance of unfamiliar social stimuli.[85] In gonadectomized male mice, exogenous estrogen significantly increased OT mRNA transcription and decreased VP mRNA transcription in the PVN of wild-type mice, while in ERβ-knockout mice, these effects disappeared completely.[28] In ovariectomized female rats, acute estradiol administration significantly decreased VP immunoreactivity in the SON and PVN after 24 hours.[86] Fetal exposure to higher testosterone resulted in a decrease in OT mRNA expression in the SON and PVN and an increase of VP mRNA expression in the SON and suprachiasmatic nuclei in adult rats, without sex differences.[87] Under physiological conditions, females secrete higher levels of estrogen than males, while males secrete more testosterone than females. Therefore, we infer that OT is more expressed and VP less expressed in females than in males in the PVN. OT is less synthesized and VP more synthesized in males. This demonstrates why it was more significant for females that OT facilitated familiar-partner preference than for males. Interactions between OT/VP and sex hormones are potential mechanisms involved in homosexuality.

OT-expression levels in females fluctuate with plasma-estrogen concentration across the estrous cycle.[88] This could be the reason that human subjects or animals included in the studies of memory were males. The majority of study results found that both OT and VP improved memory. As mentioned, estrogen increased OT levels more significantly in female brains, including in the MeA. Studies also found that gene expression of OTRs in the MeA region was essential to maintain normal social recognition in females.[89] Therefore, it is likely that OT improves memory in nonpregnant females. Gonadotropin-releasing hormone receptors were also expressed in brain regions such as the hippocampus and amygdala.[90] Chronic gonadotropin-releasing hormone–agonist application in male sheep was shown to facilitate long-term spatial memory retention.[90] However, for older men who had low testosterone levels and memory impairment due to aging, treatment of poor memory with testosterone for 1 year was ineffective.[91] As previously mentioned, testosterone increases VP expression in male brain regions, and our review concludes that VP may improve memory in males. However, various types of memory should be researched separately.

Estrogen deficiency led to anxiety- and depression-like behavior and inflammation in hippocampi in mice through *NLRP3* signaling.[92] In effect, estrogen exerted its effects on anxiety in discrepant ways, which depended on the ER subtypes: ERα was generally anxiogenic, ERβ was generally anxiolytic, and GPR30 was found both to decrease and increase anxious behaviors.[93] OT-expression levels are higher in females, due to the higher level of estrogen; however, our review found that the anxiolytic effect was more significant in males. This may well be due to the discrepant expression of ER subtypes between males and females. Previous studies on how testosterone influences anxiety were mixed, with some not finding an anyanxiolytic effect,[94] while others did.[95] Our review suggests that VP may induce anxiety in both sexes. While VP-expression level was positively correlated with testosterone, the current findings cannot explain why VP enhances anxiety in both sexes from the testosterone-expression viewpoint.

In summary, OT and VP appear to modulate social cognition via different mechanisms, many of which have interplay with sex hormones. These findings can inform future research on psychological and clinical applications.

Acknowledgments

We acknowledge Professor Chee H Ng from the Department of Psychiatry, University of Melbourne for English-language editing. This work was supported by grants from the Public Welfare Project of the Science Technology Department of Zhejiang Province (2015C33133), National Natural Science Foundation of China (81671357), National Clinical Research Center for Mental Health Disorders (2015BAI13B02), Key Research Project of Zhejiang Province (2015C03040), and National Key Research and Development Program (2016YFC1307100).

Disclosure

The authors report no conflicts of interest in this work.

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