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Minireview

From affiliative behaviors to romantic feelings: A role of nanopeptides

Jacek Dębiec*

Department of Psychiatry, New York University School of Medicine, New York, NY 10016, USA
W.M. Keck Foundation Laboratory of Neurobiology, Center for Neural Science, New York University, 4 Washington Place, Room 809, New York, NY 10002, USA

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Abstract **Love is one of the most desired experiences. The quest for understanding human bonds, especially love, was traditionally a domain of the humanities. Recent developments in biological sciences yield new insights into the mechanisms underlying the formation and maintenance of human relationships. Animal models of reproductive behaviors, mother–infant attachment and pair bonding complemented by human studies reveal neuroendocrine foundations of prosocial behaviors and emotions. Amongst various identified neurotransmitters and modulators, which control affiliative behaviors, the particular role of nanopeptides has been indicated. New studies suggest that these chemicals are not only involved in regulating bonding processes in animals but also contribute to generating positive social attitudes and feelings in humans.**

Keywords: Oxytocin; Vasopressin; Social behavior; Attachment; Emotion; Love

1. Introduction

Considering the long tradition of the humanities, the scientific pursuit of social bonds and the accompanying emotions has a relatively short record. For millennia, human cognitive and affective states were viewed independently of bodily functions. The rise of empirical science dramatically changed this situation [1]. In the second half of the 19th century, William James, one of the founders of the modern psychology, pointed at the inseparable integrity of emotions and their accompanying bodily manifestations. A few decades later, in the first half of the following century, the accumulation of data coming from brain studies lead James Papez to the formulation of the first brain-based integrated model of emotions. Although Papez theory did not get sufficient empirical support, the fact that it demonstrated a possibility that human feelings might be conceptualized in terms of well-defined cerebral circuits, stimulated a lot of research. For that reason the Papez model is considered to be a turning point in the history of affective neuroscience [2,3].

Amongst the best understood brain networks, which underlie emotions, are the circuits controlling fear and anxiety [2]. This is most spectacularly reflected through the efficacy and a wide-spread use of anxiolytic drugs. In contrast to other emotions, fear is easier to study in the brain. Fear is a ubiquitous experience in the animal kingdom and its underlying neural networks have been well-preserved in the course of evolution. Recently, however, more and more interest has been directed towards studying positive emotions and feelings, including those that accompany the human experience of romantic love [4–6].

However, love is not a scientific concept. Apparently, love is not even a distinct phenomenon. Therefore, it is impossible to empirically investigate it using a single methodology. Yet, the notion of love, as it is conveyed by everyday language, encompasses various behaviors, attitudes and affective states, which in turn may be effectively studied. Animal models of reproductive behaviors [7,8], parent–infant attachment [9,10] and pair bonding [11,12] complemented more recently by human physiological [6] and brain imaging studies [4,5] uncover neural and endocrine mechanisms that underlie these complex biological phenomena, which are associated with the human experience of love.

2. The synchrony

The survival of a species depends on its reproductive success. Reproduction, however, is a costly venture. It consumes vast amounts of energetic resources, which would be otherwise utilized on processes subserving the survival of an individual. Therefore, in the course of evolution reproductive mechanisms have been optimized in response to environmental demands [3,8]. Depending on the climatic conditions, animals exhibit various reproductive patterns. In regions with moderate climate and prolonged, regular seasonal cycles, the gonadal and thus reproductive activity harmonizes with these cycles (e.g. the gonads of seasonal breeders grow in early spring and regress in autumn). The fact that the preoptic area of the hypothalamus in these animals is an evolutionarily preserved site, which controls thermoregulation, as well as procreative functions, depicts the close relations between reproduction and seasonal changes, and indicates the role of temperature in initiating sexual activities [7]. By contrast, in more arduous environments, characterized by complete unpre-

*Fax: +1 212 995 4704.
E-mail address: jacek@cns.nyu.edu

Abbreviations: IT, isotocin; MT, mesotocin; OT, oxytocin; OTR, oxytocin receptor; AVP, vasopressin; V1aR, vasopressin receptor 1a; AVT, vasotocin

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dictability of breeding conditions, the gonads are constantly maintained at the preparedness level so breeding can immediately occur, whenever favorable circumstances arise [8].

However, successful sexual reproduction requires more than the coordination of physiological processes with the environment. Animals need to seek for, select and court their potential mate. Typically, effective mating happens, when one potential mate is receptive to the advances of the other [8]. Furthermore, in order for the fertilization to occur, insemination and ovulation have to take place in a synchronous manner. The same hormonal changes, such as alterations in estrogen and progesterone levels, which regulate the maturation of an egg, are also responsible for the enhancement of female sexual receptivity [3]. Evidence from avian studies demonstrates that seasonal variations in testosterone concentrations modulate the expansion of brain circuits that control some forms of mating behaviors in males [3]. As a result, the relevant neural circuitry, similarly to male gonads, expands in size in the springtime and recesses in the fall. In most species, sexual arousal and readiness to copulate is harmonized with peak fertility. Nevertheless, the reproductive activity of humans and few other vertebrate species does not strictly follow this pattern allowing intercourse at any time point of the cycle [3]. Consequently, courtship and mating behaviors may be expressed to some extent independently of their primary reproductive goals.

Mammalian and avian newborns are incapable of independent functioning. Therefore, it is essential that these infants receive nurturing from the very beginning. This is mainly accomplished by the formation of mother–infant attachment.

Labor and nurturing directly result from the proceeding reproductive events. The mechanisms, such as gonadotropic and gonadal hormones, which are involved in mating and pregnancy, are also responsible for initiating the maternal care of infants [3]. In many species, however, nurturance requires the cooperation of both parents. For this reason, some animals developed tools supporting the maintenance of sustained bonds between the two parents [11]. In its uttermost appearance pair bonding may reach beyond its original procreative goal and take a form of a life-long monogamous relationship [11]. Reproductive behaviors, mother–infant attachment and adult–adult bonding require the harmonization of numerous neural and endocrine factors. Increasing amounts of data depict the critical role of the two peptides oxytocin (OT) and arginine vasopressin or vasopressin (AVP) in modulating these three dimensions of mammalian social functioning.

3. Nanopeptides

Oxytocin and vasopressin are nanopeptides (nine amino-acid peptides) (Fig. 1). In general, nanopeptides are key homeostatic molecules responsible for the control of osmotic pressure in terrestrial vertebrates. Both peptides are synthesized in the paraventricular and supraoptic nuclei of the hypothalamus, and subsequently transported through the projections ending in the posterior pituitary (neurohypophysis). Neurohypophysis is the storage site, from which OT and AVP are released to the circulation. In addition, vasopressin is also produced in the suprachiasmatic nucleus of the hypothalamus and in the bed nucleus of stria terminalis and the medial amygdala [13]. These sites send exclusive intra-cerebral projections. Oxytocin is also delivered to the specific sites in the central nervous system. Distinct projections from the paraventricular nuclei transport OT to the hypothalamus, amygdala, hippocampus, nucleus accumbens, as well as the brain stem and spinal cord structures [12]. Major peripheral roles of OT involve supporting uterine contractions throughout labor and ejection of milk during lactation [12,14]. In contrast, vasopressin exerts powerful anti-diuretic action by controlling water reabsorption in kidneys.

The nanopeptide family involves both vertebrate and invertebrate peptides, which suggests that the ancestral gene encoding the precursor peptide was already present around 700 million years ago, before the two groups separated [15]. The descendant peptides developed from their predecessor by a gene duplication mechanism [15,16]. All vertebrates, except primitive cyclostomes (jawless fish), possess both OT-like and AVP-like molecules, which represent two ancestral lines [16]. The most likely precursor of oxytocin is isotocin (IT), which may be found in bony fish [15]. Mesotocin (MT), which is present in amphibians, reptiles, birds and some marsupials, represents an intermediate form between IT and OT. The

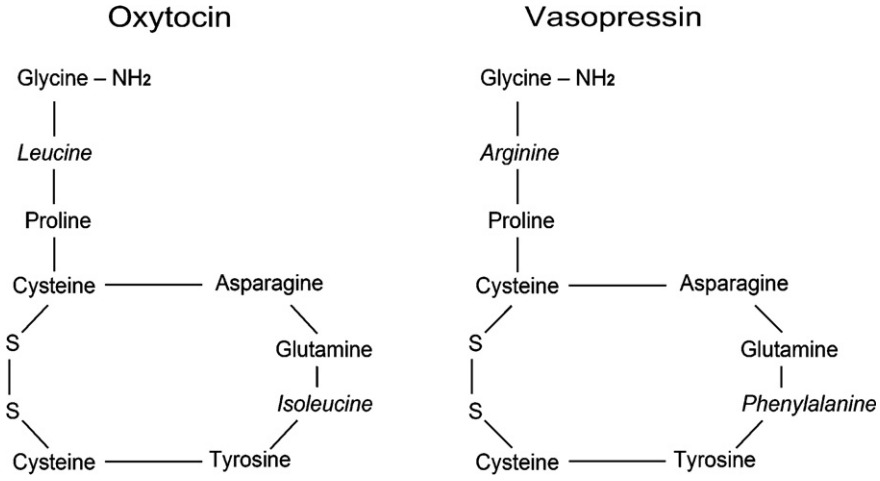

Fig. 1. Chemical structures of oxytocin and vasopressin. Oxytocin and vasopressin are nine-amino peptides (nanopeptides) and differ only by two amino acids (marked in italic).

hypothesis of an intermediary character of mesotocin is supported by the fact that it is also present in lungfish, the closest relatives of the Devonian lobe-fin fish group, from which amphibians evolved [15,17]. On the other hand, some pouched mammals possess both MT and OT [15]. Arginine vasotocin or vasotocin (AVT), found in all classes of vertebrates, is a non-mammalian analogue and a precursor of vasopressin [18,19]. The evolutionarily conserved structure suggests that the basic function of nanopeptides, such as the control of osmotic pressure, has been also preserved [15]. The supporting evidence comes from cartilaginous fish, which use alternative osmoregulatory mechanisms. These animals synthesize a variety of nine amino-acid peptides, such as glumitocin, aspargtocin, valitocin and other [15].

4. Amorous liaisons and their chemicals

Apart from their homeostatic role in osmoregulation, nanopeptides are commonly involved in modulating reproductive behaviors. This function emerged early in the process of evolution and is already present in bony fish, which synthesize ancestral peptides – isotocin and vasotocin. For example, a recent study demonstrates that exogenous IT stimulates an approach toward visual stimuli of conspecifics in male goldfish, whereas an administration of AVT produces an opposite effect [20]. Isotocin and vasotocin are also implied in the modulation of other piscine mating behaviors, such as sex-typical vocalizations [19].

Ascending the evolutionary tree, more evidence of the involvement of the nanopeptides in the animal courtship can be observed. Amphibian studies show that AVT enhances responding to sexual stimuli in olfactory, visual and tactile modalities [21]. For instance, by increasing secretion of male pheromones in salamanders, vasotocin augments female receptivity [7]. In addition, exogenous AVT potentiates male behavioral reply to sexually mature females seen through the glass [21]. Furthermore, an administration of AVT in amphibians increases a clasping behavior (embracing a female by a male with his fore and hind legs) triggered by a tactile stimulation in the cloacal region [21]. The enhancing effects of the nanopeptide on the responses to the arousing stimuli involve lowering the threshold of the stimulus processing, as well as direct actions on motor pathways, which control the behavior [7,21]. This is accomplished by a discrete distribution of the neuropeptide-containing cells and the relevant peptidergic receptors. It has been demonstrated by numerous studies across various vertebral taxes that these two factors are regulated by gonadal hormones, [7,18,21,22]. Consequently, this form of regulation leads to a sexually dimorphic expression of neuropeptides and their receptors in the brain [21]. For example, the rise of testicular hormones (testosterone, dihydrotestosterone) levels in the circulation boosts concentrations of AVT and its receptors in the male bullfrog's vocalization centers [18]. This, in turn, increases a frequency of the mate calls. Analogous estradiol-driven changes in the female frogs facilitate the phonotaxis – an approach to the source of the advertisement calling [18,21]. Thus these differences in the expression of peptidergic cells may underlie sexually complementary functions.

Sexually dimorphic distribution of nanopeptides in the brain with resultant functional consequences is well-manifested in mammalian species. Although vasopressin and oxytocin are important modulators of reproductive behavior in both sexes, AVP seems to be more critical for various aspects of male sexuality, whereas OT is a key factor controlling female sexual responses [3]. This is best demonstrated by rodent studies, which indicate vasopressin's involvement in male courtship, as well as territorial scent marking and intermate aggression [3]. In contrast, oxytocin has been indicated in mediating female receptivity, such as displaying a characteristic arch-backed lordosis posture, which permits mounting, intromission and ejaculation by a male [3].

Human research demonstrates that OT and AVP are implied in human sexual response [23]. Both peptides are released into circulation during arousal in men and women [23]. Studies using continuous plasma sampling through indwelling catheters reported significant increase of OT levels during orgasm in both sexes [24,25]. The rise of plasma oxytocin positively correlated with the intensity of orgasmic contractions as measured by anal electromyography [25]. Interestingly, one study with human male subjects revealed distinct temporal characteristics of the peptide release [26]. It has been reported that sexual arousal leads to an increase of circulating AVP, which returns to baseline at a time of ejaculation. In contrast, OT levels rise during ejaculation and reach baseline around 30 min later [26]. This pattern of findings suggests different contributions of the neurohypophyseal peptides to the regulation of sexual response. A recently published animal study demonstrates that through modulating the GABA-ergic inhibition AVP and OT have opposite effects on the amygdala activity, with vasopressin exciting and oxytocin reducing the amygdala activation [27,28]. The amygdala is a key structure in the emotional processing [2]. It has been also implied in human sexual response [29–31]. Therefore, it may be speculated that changes in AVP and OT concentrations during sexual stimulation and orgasm affect the amygdala activity and thus modulate the level of excitation during intercourse, and in the postcoital period.

However, copulation is not the only source of oxytocin surge in mammals. Vaginocervical stimulation during labor and suckling throughout lactation are both very potent triggers of OT release from the posterior pituitary in females [14].

5. Born to be loved

The development of mother–infant bonds is often essential for the survival of the offspring. Many mammalian species display potent maternal behavior right away after parturition. Typically, predator species, which are born relatively immature and require a long-term parental care, may form bonds for a longer period of time following the delivery [3]. In contrast, prey species are born capable of locomoting (in order to escape the predator) and may get easily separated from their parents. Therefore, these species develop mother–infant bonds very quickly [3]. However, despite the temporal differences in the bonding patterns, the underlying neurochemistry seems quite similar across mammalian species [3].

Strongly expressed maternal behavior makes sheep a very useful model of attachment [12]. Contrary to other species, such as rodents, which easily accept strange new pups to their nests, sheep and other ungulates display a highly selective maternal behavior [3]. The rapid development of mother–infant attachment suggests the critical involvement of events

occurring during pregnancy and labor. Indeed, hormonal priming with estradiol and progesterone in conjunction with OT release during vaginocervical stimulation are effective in inducing maternal behavior in virgin ewes [9]. What is more, these same treatments reverse the existing rejection behavior towards alien lambs [9]. Similar effects of the neurohypophyseal peptide may be observed in the rat model of attachment, where intra-cerebral infusions of OT trigger maternal behavior in virgin females [10]. Yet, oxytocin seems to be critical only during bonding with the firstborns. The disruption of oxytocinergic transmission when bonds with the firstborn pups are already established or following subsequent pregnancies has no effect on maternal tendencies [3].

Based on animal models, it has been hypothesized that hormonal priming during pregnancy stimulates in mammals the synthesis of oxytocin and upregulates the expression of its receptors in the relevant brain areas: the medial preoptic area, the ventral tegmental area, the bed nucleus of stria terminalis, the amygdala and the olfactory bulb [3,12]. As a result, the potentiated oxytocinergic activity harmonized with the action of other neurochemicals, such as prolactin, norepinephrine, acetylcholine, glutamate and GABA contributes to the establishment of memories of the infant and the associated attachment [3,12].

Nevertheless, nurturing in mammals often involves both parents. This requires not only the development of parent–infant attachment but sometimes necessitates the bond-formation between the two parents.

6. A little romance on the prairie

The prairie vole, better than any other species, enables us to study the brain mechanisms of adult–adult bonding. Following mating, these rodents form enduring, monogamous relationships with their mates [11,12,32]. Moreover, after losing their companion, prairie voles generally do not again attach to a new partner [11]. In contrast, closely taxonomically related montane voles do not bond with each other. Comparative studies of these two species, which display distinct affiliative patterns, provide insight into the neurochemistry of social bonding [11].

Numerous studies indicate the vital role of vasopressin and oxytocin in the formation of partner bonds in prairie voles [11,12]. Either of the neurohypophyseal peptides infused into the vole's brain facilitates pair bonding in males and females, even in the absence of mating [11,12]. Congruently, post-mating blockade of peptidergic receptors impairs subsequent bond formation in prairie voles [11,12]. Oxytocin seems to be more involved in bonding in females, whereas vasopressin in males [11]. However, the presence of these peptides in the brain is not sufficient to promote the establishment of an adult–adult relationship. The augmentation of peptidergic transmission using exogenous AVP or OT has no influence on boding in nonmonogamous montane voles [11]. These findings led researchers to investigate the distribution of oxytocin and vasopressin receptors in the brains of both rodent species. Indeed, in comparison to montane voles, their monogamous cousins have higher densities of oxytocin receptors (OTRs) in the nucleus accumbens, bed nucleus of stria terminalis, and the lateral amygdala [33]. Additionally, in comparison to their promiscuous relatives, prairie voles are characterized by an increased expression of vasopressin receptor 1a (V1aR) in the ventral pallidum and the medial amygdala [34]. A recent study, using viral-mediated gene transfer, demonstrates the crucial role of the peptidergic receptor distribution in shaping social behavior of the voles [35]. By means of viral vectors, promiscuous voles were engineered to express V1aRs in a manner similar to their monogamous relatives. This manipulation facilitated partner bond formation following mating in the species that do not naturally bond [35]. Thus the alteration of vasopressin receptor distribution may produce major behavioral changes, which profoundly affect social behavior.

7. Addicted to love

The amygdala is an important structure in processing social signals, such as individual-specific olfactory "fingerprints" in rodents [36]. Previous research has demonstrated that peptidergic activation in the rodent amygdala is critical for the recognition of conspecifics or social learning [11]. For example, OT knockout mice selectively fail to express memory for previously encountered conspecifics [36]. However, intra-amygdala infusions of oxytocin are sufficient to restore social learning in these transgenic rodents [36]. Similarly, blocking of either OTRs in the nucleus accumbens or V1aRs in the ventral pallidum impairs partner recognition in rodents [11].

The nucleus accumbens and the ventral pallidum, which receive projections from the amygdala, are crucial components of the brain dopaminergic reward–learning system [11,12,32]. For instance, animal models demonstrate the involvement of either of these structures in substance abuse and addiction [32]. Therefore, it has been hypothesized that the release of oxytocin and vasopressin during mating reinforces social signals by linking them to the dopamine reward pathways [32]. In fact, blocking the dopamine D2 receptor impairs, whereas activating it induces partner bonding in prairie voles [32]. Animal data provide evidence that the formation of mother–infant attachment also involves dopamine reward systems [12,32]. Neurohypophyseal peptides in concert with dopaminergic reward circuits may thus in a similar fashion contribute to the establishment of distinct forms of bonding (Fig. 2).

8. What about the feelings?

As it has been shown by numerous studies, vasopressin and oxytocin are implied in mammalian reproductive responses,

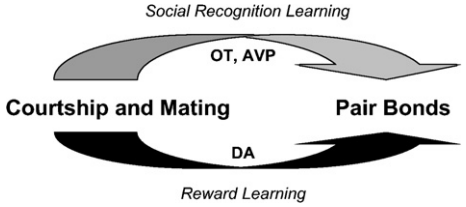

Fig. 2. The convergence of social recognition learning and reward learning systems in the formation of pair bonds. The concurrent activation of peptidergic social learning pathways and dopaminergic reward pathways reinforces partner approach behavior and pair bonds [11,32]; OT, oxytocin, AVP, vasopressin, DA, dopamine.

mother–infant attachment and pair bonding. In humans, all these social behaviors are usually accompanied by associated emotions and feelings, such as the feeling of love [6]. Therefore, the question arises whether nanopeptides play a role in modulating human affective states. Indeed, recent studies demonstrate the possible involvement of oxytocin in romantic feelings, as well as in controlling prosocial behaviors in human subjects [6,37].

In one study, Gonzaga et al. instructed participating heterosexual romantic couples to talk about their first date in order to trigger romantic feelings [6]. The interaction between the partners was videotaped and affiliation cues displayed during this conversation were assessed. The partners were then asked to report their own emotions and estimate the emotions of their partner. The researchers observed that the momentary experiences of romantic love have characteristic nonverbal displays, such as affirmative head nods, smiles, gesticulation and leaning toward partner [6]. These behavioral displays were distinct and did not occur during expression of other emotions (e.g. embarrassment, amusement or anxiety) [6]. In a subsequent experiment, the subjects were asked to recall the event that triggered the romantic feeling. Several blood samples were taken during this process in order to assess the levels of oxytocin. The authors found that OT levels were positively related to the behavioral displays of love [6]. Consistent with animal studies, oxytocin may thus play a role in human feelings, which are associated with commitment.

In another human study, researchers investigated the influence of exogenous OT on prosocial behaviors [37]. OT is known to reduce stress and anxiety in animals [28,38]. Kosefeld et al. designed an experiment, in which male volunteers were given a task to invest a sum of money with another player [37]. Before making their decisions, one group of subjects received intranasal oxytocin, whereas another group received placebo. The authors found that exogenous OT as compared to placebo increases trust resulting in the willingness to invest larger amounts of money with an anonymous player. In addition, this effect of the nanopeptide was not due to the augmented tendency for risk behaviors [37]. Intranasal OT is known to cross the blood–brain barrier [37]. Therefore, the effects of the peptide may be attributed to its action in the brain. Kosfeld et al. are the first to publish a report showing that oxytocin may modulate human prosocial behavior by increasing trust [37]. Nevertheless, their study does not reveal neural mechanisms, which are involved in OT's action. One possibility is that the neuropeptide increases trust by decreasing social fear. This may be achieved by acting on the amygdala, the key site of emotional processing and social learning [2,28,39]. A recently published study addressed this issue: using intranasal OT and functional magnetic resonance imaging, Kirsch et al. investigated an influence of this peptide on brain activity in response to social fear stimuli, such as angry or fearful faces [40]. Previous studies demonstrated that looking at angry or fearful faces activates the amygdala in human subjects [40]. Kirsch et al. observed that exogenous oxytocin reduces amygdala activation triggered by an exposure to social fear signals. More interestingly, the same experiment revealed that the nanopeptide was also effective in attenuating the functional connectivity between the amygdala and the brain stem structures, which are involved in mediating autonomous fear responses [2,28]. This suggests that oxytocin may facilitate prosocial attitudes in humans by calming fear. Whether this mechanism contributes to an experience of romantic feelings remains unknown.

9. Till death do us part

The example of prairie voles demonstrates that social recognition memories and associated pair bonds may produce life-long behavioral effects. However, the monogamous social structure as illustrated by prairie voles characterizes only 3–5% of mammalian species [11]. In most mammals pair bonding is closely related to its reproductive goal and resolves once this goal is achieved. The question arises whether an enduring character of social relationships in voles and other species results only from the initial bond formation or whether there are other mechanisms that maintain already established bonds. It has been proposed that peptidergic stimulation during mating strengthens social recognition memories and the resultant partner approach behavior by linking them to the dopamine reward circuits [32]. Yet, the question remains whether interactions between the reward and social learning systems are also required for supporting the existing bonds. So far there is no answer to this question. However, studies of other learning systems suggest that the persistence of learned behaviors in animals may depend not only on the mechanisms subserving the initial formation of memories but also on the mechanisms, which actively maintain existing memories [41,42].

Numerous studies indicate that the development of long-lasting memories requires an activation of cascades of molecular processes, which involve stimulation of receptors at synapses, initiation of second messengers and transduction pathways, as well as gene expression and synthesis of new proteins [42,43]. These processes are referred to as memory consolidation and lead to the modification of synaptic connections [42,43]. Various types of learning, including social and reward learning undergo consolidation [38,44]. For long, it has been believed that consolidation occurs only once in a life of a memory [43]. However, increasing number of data demonstrates that reactivation of the memory through retrieval by presenting a learned cue initiates cascades of molecular processes called reconsolidation, which when augmented enhance the learned behavior [45] but when disrupted may lead to lasting memory deficits [46–49]. Reconsolidation only in part recapitulates consolidation [41,42]. Interestingly, emotional learning, such as fear learning, which often produces life-long responses to stimuli that were associated with the original threatening event, undergoes reconsolidation processes and thus may be augmented or impaired [45,50]. It has been recently demonstrated that learned reward-seeking behaviors [48,49], as well as social recognition memories undergo reconsolidation [51]. Animal studies indicate the involvement of neurohypophyseal peptides in consolidation processes [28,38]. The question arises whether peptidergic transmission is also involved in memory reconsolidation and thus implied in maintaining existing memories and learned behaviors, such as partner preference. Furthermore, it is well-established that the expression of peptidergic cells in the brain is controlled by gonadal hormones [7,18,21,22]. Therefore, it remains to be answered whether changes in ovarian and testicular hormones levels influence existing social bonds and associated behaviors. An existence of plausible mechanisms supporting the maintenance

of established bonds may help to explain why certain relationships last life-long, whereas other do not.

10. Conclusions

The scientific pursuit of the mechanisms underlying social emotions and behaviors reveals the critical role of neurohypophyseal peptides oxytocin and vasopressin. So far, however, most of the findings come from animal models. It has not been determined whether the same mechanisms control human and rodent pair bonding [11]. Another difficultly, related to human studies is that systemic drug administration, such as intranasal OT may produce its effects anywhere in the organism. Yet, animal studies help to identify peptidergic circuits in the brain. These findings may be subsequently applied in human functional brain imaging experiments.

Translational research of the social brain is getting us closer to the understanding of the matter of love.

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