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The chemistry of love

Some is known about animals - what is true for humans?

We use the word love in many ways: to describe the attraction between two individuals, to describe the physical sexual act between two individuals, to describe the bond between the mother and the father and their child, or to describe the bonds between members of a family or closed society. These different types of love between human beings are, of course, in many ways interrelated.

Love has been a theme for poets/authors since mankind started to communicate. We have enjoyed reading how it is to be in love, but have been spared a molecular explanation of what happens in our brains! During the last century, the knowledge of human physiology and chemistry has expanded from a rather vague knowledge of basic processes of the body to a detailed knowledge down to the level of molecules and atoms. Subjects like human reproduction have been studied in detail. The field of love, and the chemical and neurological processes in the end leading to a wish to reproduce, has apparently, and not surprisingly, been a field of research of low priority. However, during the last ten years, scientists and journalists have discussed various aspects on the chemistry of love, and the importance of pheromones, phenylethylamine and other compounds and physiological events for human love in television programmes, newspapers and magazines. When scrutinizing the various claims, it is apparent, that many "true facts" are hypothetical theories, and that in many cases observations made on animals have directly been transferred to the human world. It is sometimes surprisingly difficult to find scientific information and scientific publications related to this field in research bases like Pubmed and PsycINFO. The information in this paper should be read with this knowledge, but also with an open and humble mind. This is a difficult but very important field of research.

We can identify several components in love between living creatures. Some scientists have chosen to describe the process of falling in love as a three-stage rocket: Lust, Romantic attraction and Attachment [1]. During this process several neurological and biochemical systems will be engaged and interact. Although these three components are here described as interrelated, they may also be described as isolated phenomena.

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It appears that the initial attraction, *Lust*, between two individuals is basically influenced by some simple anatomic facts. Thus males are attracted to women with, *e.g.*, low waist to hip ratio and low age of face [2]. The attraction of women to males varies across the menstrual cycle, a woman, *e.g.*, preferring a symmetrical "masculine" face during the fertile phase of her menstrual cycle [3]. This immediate interest is modified as soon as the couples get contact by all well-known factors like body language, speech, culture, shared interests etc. This would add the process of *Romantic Attraction* to the feeling of *Lust*.

Pheromones

Classically, a pheromone is defined as a substance excreted by an animal to the outside of that animal, which is then received by another individual of the same species, which then elicits some behavioural response related to the survival of the species. According to popular concepts, pheromones "go in action" once the couples approach each other (or, *e.g.*, get exposed to a piece of clothing that the partner has worn). However, there is today no consensus of the role of pheromones in humans. There are many quite convincing reports describing the effects of pheromones on the menstrual cycle [4] on the olfactory recognition of the newborn by its mother [5], and of the olfactory signal of the maternal breast odour to the infant [6]. Studies with synthesized human male hormones have been shown to affect the sexual attractiveness of men to women [7], and with synthesized putative female pheromones likewise to increase the attractiveness of women to men [8]. It

has been suggested that androgen steroids act like pheromones in humans [9]; however, no bioassay - guided study has led to the isolation of true human pheromones [5]. In animals, the vomeronasal organ (VNO) is the putative receptor of pheromones. Numerous studies have failed to prove that the VNO is functional in human [10,11]. Given the combined evidence, it may be so, that at least some pheromonal effects exist in humans and that as a possible, but not proven, receptor organ remains the olfactory epithelium. It should also be mentioned, that olfactory receptors genes are expressed in the testes, suggesting a chemosensory mechanism at the level of sperm selection [11].

Phenylethylamine (PEA), dopamine and serotonin

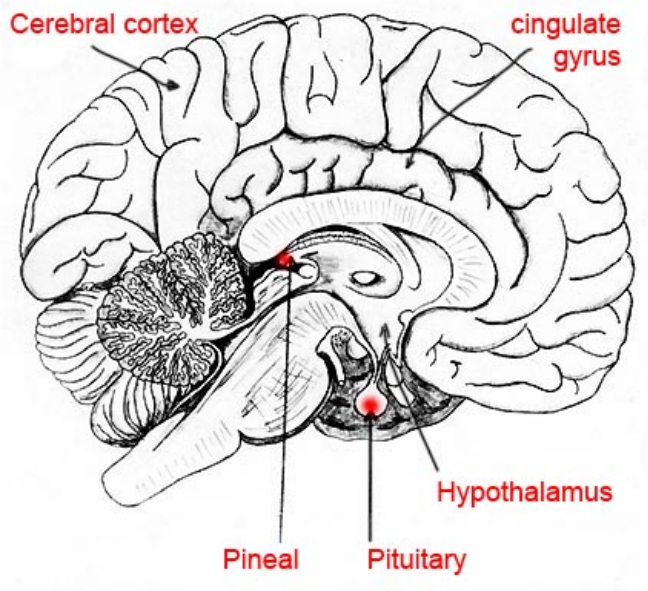
PEA is an amphetamine-related substance belonging to the "Ecstasy" group and has in numerous popular publications been named "the molecule of love" (not to be confused with the party drug MDA, "love"). Few, if any, up-to-date scientific publications can be found related to this subject, with the exception of a recent essay [12]. It is suggested that PEA increases "warmth, affection, sexuality and the feeling of physical energy". It is suggested that this neurotransmitter increases when an individual falls in love, and that this amphetamine-like substance will give the individual who has fallen in love a kick, a reward. It has also been suggested that chocolate, which contains PEA, will give the same kick [13]. This is unlikely, taking the small amounts of PEA in chocolate in consideration, and the short half-life of the substance [12]. It has also been suggested that the amphetamine-like effect of PEA will diminish with time, explaining why some relations fade away in some years (1-4 years, cf. "7-year-itch"). In summary, the thought of a role of PEA in human love is fascinating, but so far speculative.

Dopamine levels have been reported to be increased when an individuals is in love [12], findings in agreement with neural correlates in functional MRI scanning, see below. The role of serotonin is poorly understood. It is known that selective serotonin uptake inhibitors (SSRI) may affect libido and orgasm; this problem may be less pronounced in highly selective SSRI [14].

Brain activity when in love, as investigated by Functional Magnetic Resonance (fMRI)

The activity of the brains of 17 individuals who were deeply in love was investigated using the technique of fMRI. The individuals were investigated while viewing pictures of their partners, and of pictures of three friends of similar age, sex and duration of friendship. The activity recorded while watching their partners was similar to all individuals and surprisingly restricted and unique, being located to foci in the medial insula and

the anterior cingulated cortex, and subcortically, in the caudate nucleus and the putamen, all bilaterally. Some of these regions are implicated in happy states and social interactions [15]. Similar studies have been performed with mothers and their children. Interestingly, brain areas rich in oxytocin and vasopressin receptors (see below) are shown to be active when the mothers look upon pictures of their own children but not the children of other women [16].



Neuroendocrinology of sexual arousal and orgasm

Sexual arousal will produce transient sympathoadrenal activation with increases of plasma epinephrine and norepinephrine [17]. The increase of oxytocin and vasopressin after copulation reported for animals has so far not been shown beyond doubt to occur in humans [18]. Prolactin is secreted after orgasm [18], and it is suggested that it will take part in a feedback control of sexual drive [19].

Vasopressin and oxytocin. The hypothalamic - pituitary - adrenal (HPA) axis

Recently, these pituitary hormones have attracted the attention as being of possible importance in establishing long-lasting bonds between humans, Attachment. If we discuss Attachment in the simple terms of the popular three-stage love theory it has been suggested that vasopressin (for males) and oxytocin (for females) will create a bond to keep the man and women together when the Romantic Attraction has faded away, and, according to the speculative PEA theory, when there is no longer any amphetamine-like reward in the relationship. While oxytocin is secreted during labour and vasopressin is of importance in fluid balance, these hormones may also increase during touch and caress, and, maybe in humans, during intercourse (see above).

Positive social behaviours, including social bonds and attachment may, furthermore, diminish the activity of the HPA axis. Interestingly, vasopressin and oxytocin have been implicated in the control of the HPA axis (20).

The great interest in vasopressin and oxytocin in relation to attachment has originated in a series of fascinating studies of the prairie vole [21, 22]. Vole species display a wide range of social behaviour, ranging from being highly social and monogamous to being solitary and promiscuous. Social bonds form after sexual activity, and behaviours associated with monogamy, including pair-bond formation are facilitated by vasopressin

binding to a receptor in the ventral pallidal region. If sexual activity is prevented, a bond can be created by injecting vasopressin. In one experiment, administration of vasopressin receptor antibodies prevented the creation of bonds. In another experiment, the density of vasopressin receptors in the ventral pallidal region was increased by delivering the receptor gene using an adeno-associated vector. These males exhibited an increase in pair-bond formation compared to controls.

Thus, these and other experiments show that vasopressin and oxytocin are important in the creation of bonds in non-human mammals, and for the first time, scientist have succeeded in changing the behavioural pattern by introducing hormone receptors in the brain. The question is - do vasopressin and oxytocin circuits play the same role in humans. Does the surge in oxytocin during labour play a role in creating maternal love and bonds between mother and child? Has a possible increase in vasopressin/oxytocin during intercourse any significance? More important, will couples who live together, have children together, care for each other, use these circuits in creating bonds and long-lasting relations? As pointed out in an essay in *Nature* commenting the vole studies of the Larry Young laboratory [23], there are other important questions related to this subject. Lower-quality day care may alter infant attachment and cortisol patterns; what will happen later in life? Severely deprived children, who have lived their entire life without love, may exhibit abnormalities in later relationships. We may in cases like this improve our knowledge and possibility to help the children by brain imaging and neurobiochemical studies.

We are just in the beginning in understanding the chemistry of love in humans and there are many question marks? Which role do pheromones, PEA and oxytocin/vasopressin play in human love life? We know, however, that the power of love in humans is great. Lust and romantic attraction can affect us in unpredictable ways, and make everyone act irrationally. The studies of attachment are of interest in a broader sense, in that we not only are dealing with human beings in love, but also with attachment between individuals in the society. These studies have focused interest on the chemistry and brain function in interaction between individuals, a new and important field of research.

References

1. Fisher H.E., Aron, A., Mashek, D., Li, H. and Brown., L.L. (2002) Defining the brain systems of lust, romantic attraction and attachment. Archives of sexual behaviour 31 413-419.

2. Furnham, A., Mistry, D and McClelland A. (2004) The influence of age of the face and the waist to hip ratio on judgements of female attractiveness and traits. Personality and Individual Differences 36 1171-1185.

3. Gangestad, S.W., Simpson, J.A., Cousins, A.J., Garver-Apgar, C.E. and Christensen, N.P. (2004) Women´s preferences for male behaviour displays change across the menstrual cycle. Psychological Science 15 203-207.

4. Preti, G., Wysocki, C.J., Barnhart, K.T., Sondheimer, S.J. and Leiden, J.J. (2003) Male axillary extracts contain pheromones that affect pulsatile secretion of luteinizin hormone and mood in women recipients. British Journal of Dermatology 68 2107 - 2113.

5. Wysocki, C.J. and Preti, G. (2004) Facts, fallacies, fears and frustrations with human pheromones. The Anatomical Record Part A 281A 1201 -1211

6. Porter, R.H. and Winberg, J. (1999) Unique salience of maternal breast odors for newborn infants. Neuroscience and Biobehavioural Reviews 23 439 - 449.

7. Thorne, F., Neave, N., Scholey, A., Moss, M. and Fink, B. (2002) Effects of putative male pheromones on female ratings of male attractiveness: influence of oral contraceptives and the menstrual cycle. Neuroendocrinological Letters 23 291 - 297.

8. MacCoy, N.L. and Pitino, L. (2002) Pheromonal influences on sociosexual behaviour in young woman. Physiology & Behaviour 75 367 - 375.

9. Pause, B. (2004) Are androgen steroids acting as pheromones in humans? Physiology & Behaviour 83 2 - 29.

10. Keverne, E.B. (2002) Phermones, vomeronasal function, and gender-specific behaviour. Cell 108 735 - 738.

11. Keverne., E.B. (2004) Importance of olfactory and vomeronasal systems for male function. Physiology & Behaviour 83 177 - 187.

12. Shaik, S. (2003) Chemistry - A central pillar of human Culture. Angewandte Chemie - International Edition 42 3208-3215.

13. Benton, D. and Donohoe, T.R. (1999) The effects of nutritients on mood. Public Health Nutrition 2 -403 -409.

14. Pallanti, S. and Koran, M.L. (1999) Citalopram and sexual side effects of selective serotonin reuptake inhibitors.American Journal of Psychiatry 156 796.

15. Bartels, A. and Zeki, S (2000) The neural basis of romantic love. NeuroReport 11 3829 - 3834.

16. Bartels, A. and Zeki, S. (2004) The neural correlates of maternal and romantic love. NeuroImage 21 1155 - 1166.

17. Exton, M.S., Krüger, T.H.C., Koch, M., Paulson, E., Knapp, W., Hartman, U and Schedlowski, M. (2001). Coitus-induced orgasm stimulates prolactin secretion in healthy subjects. Psychoneuroendocrinology 26 287 - 294.

18. Krüger, T.H.C., Haake, P., Chereath, D., Knapp, W., Janssen, O.E., Exton, M.S., Schedlowski, M. and Hartman, U. (2003) Specificity of the neuroendoccine response to orgasm during sexual arousal in men. Journal of Endocrinology 177 57 - 64.

19. Krüger, T.H.C., Haake, P., Hartman, U., Schedlowski, M. and Exton, M.S. (2002) Orgasm-induced prolactin secretion: feed-back control of sexual drive. Neuroscience and Biobehavioral Reviews 26 31 - 44.

20. Carter, C.S. (1998) Neuroendocrine perspectives on social attachment and love. Psychoneuroendocrinology 23 779 - 818.

21. Pitkow, L.J., Sharer, C.A., Ren, X., Insel, T.R., Terwilliger, E.F. and Young, L.J. (2001) Facilitation of affiliation and pair-bond formation by vasopressin receptor gene transfer into the ventral forebrain of a monogamous vole. Journal of Neuroscience 21 7392 - 7396.

22. Lim, M.M., Wang, Z., Olazabal, D.E., Ren, X. Terwilliger, E.F. and Young, L.J. (2004) Enhanced partner preference in a promiscuous species by manipulating the expression of a single gene. Nature 429 757 - 757.

23. Konner, M. (2004) The ties that bind. Attachment: the nature of the bonds between humans are becoming accessible to scientific investigation. Nature 429 705.