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Endocrine Factors of Pair Bonding

Stárka L.
Institute of Endocrinology, Prague, Czech Republic

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Mailing Address: Professor Luboslav Stárka, MD., MSc., DSc., Institute of Endocrinology, Národní 8, 116 94 Prague 1, Czech Republic; e-mail: lstarka@endo.cz

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Abstract: Throughout literature – fiction and poetry, fine arts and music – falling in love and enjoying romantic love plays a central role. While several psychosocial conceptions of pair attachment consider the participation of hormones, human endocrinology has dealt with this theme only marginally. According to some authors in addictology, falling in love shows some signs of hormonal response to stressors with changes in dopamine and serotonin signalling and neurotrophin (transforming growth factor b) concentration. Endorphins, oxytocin and vasopressin may play a role during the later phases of love. However, proof of hormonal events associated with love in humans has, until recently, been lacking.

Love is perhaps the unique most common theme found in classic literature and an important motif in other arts, however, the basis of love has escaped explanation by art and science. Relationships between partners, from falling in love and forming a pair to separation, domestic violence and other extreme behaviour patterns have been a concern for law, sociology and psychology, but medicine and biochemistry have until recently only superficially mapped out these phenomena. There is only a remarkably modest collection of scientific literature concerning the role of hormonal changes in how people fall in love [1, 2, 3]. Using the internet search program PubMed, searching for "love AND hormones" returns about 40 results, which for the most part, as far as the theme of relationships is concerned, are irrelevant.

Neither science nor classic literature has provided a real answer as to the question of what love actually is, despite the indubitable importance of this psychosocial phenomenon. According to Jankowiak of the University of Las Vegas [4], romantic love can be found in 147 of 166 different cultures, which they studied. It is a nearly universal phenomenon, and very a common, even if not absolutely necessary part of human biological reproduction. Being in love represents, in many cases, the opening of a long-term partnership. Some researchers, however, do not place love into the same category of basic primitive human emotions such as fear, anger or pleasure.

Love being guided by – perhaps even caused by – actual events occurring in the central nervous system can now be better understood thanks to modern techniques, such as magnetic resonance tomography, which has made it possible to monitor neurological events in specific brain areas of a person experiencing love. Unfortunately, even studies using these techniques aren't much extensive [5, 6] and offer only the conclusion that the brain areas, which undergo activation and deactivation, are the same, which concern general emotions. The activity was restricted to foci in the medial insula and the anterior cingulate cortex and, subcortically, in the caudate nucleus and the putamen, all bilaterally. Deactivations were observed in the posterior cingulate gyrus and in the amygdala and were right-lateralized in the prefrontal, parietal and middle temporal cortices. The combination of these sites differs from those in previous studies of emotion,

suggesting that a unique network of areas is responsible for evoking this affective state. In another study [7] activation specific to the beloved occurred in the right ventral tegmental area and right caudate nucleus, dopamine-rich areas associated with mammalian reward and motivation. Love thus involves a specific neural network that surpasses a dopaminergic-motivation system. However, we still know very little about what influences, which transmitters or hormones take part in this process. Here should be emphasized that love is not identical with sexuality and sexual function. These are also controlled by a handful of hormones, e.g. testosterone controlling libido and sexual arousal, prolactin, which is inhibiting sexual function, or a set of hormones, transmitters and active compound used for improvement of sexual dysfunction. Hormonal influences on sexual functions and sexual activity are not the object of this review.

There are many studies about love, which have concerned with psychosocial or cultural aspects; many tests are focused on neurobiological aspects of love in animals during courtship. Experiments have shown that the formation of a biological pair is largely defined by the hypothalamus-pituitary-adrenal axis and the oxytocin axis [8, 9]. The attempt to understand better the endocrine mechanism behind love in humans should, however, in no way degrade this phenomenon to a simple chemical process.

Love is very strongly anchored in the evolutionary history of man, in his biology and biochemistry [10]. Of course, love is deeply programmed into our genes due to the fact that it helps to keep partners together during the period of time necessary for raising offspring until the first signs of the offspring's ability to survive independently. Unfortunately for us, this genetically anchored period is limited approximately to a mere 4 years. This "four year attraction" has shown a marked impact on recent divorce statistics: this impact was seen in the majority of the 62 cultures studied by H. Fisher [11]. A clearly defined peak in divorces occurred in the fourth year of marriage. Additional child noticeably moved the peak in divorces to the seventh year of marriage. Other evidence shows that romantic love generally doesn't last more than one year [12].

Romantic love is neither eternal nor exclusive and it is therefore necessary to observe it as a dynamic process. Unlike poetic love in art, it is not a special condition of the heart or soul. From the perspective of endocrinology it is more a game of hormones and transmitters, and according to certain authors it is even an actual chemical intoxication of the organism. It shouldn't come as a surprise that for some people love can actually be stressful, because the chemical pathways and hormonal factors involved in love are actually very similar to those involved in stress.

Theories have been proposed that hormones play a very limited role [11, 13, 14, 15]. It has also been proposed that love is parallel to the processes of addiction, which are also rather unclear with the neurohormones playing an important role [16].

3 Phases of Love

Many authors hold a view of the love being divided into three different phases. During the phase of fulfilment and in its final phase, its main task is the reproduction and care of offspring.

As concerns the romantic love, it is the dominant belief that catecholamines – adrenaline, noradrenaline, and their metabolites – and also the stress steroid hormone cortisol and its regulators – corticoliberin and adrenocorticotropic hormone ACTH – play the main role. In the phase of fulfilment the major role probably assume endorphins, endogenous polypeptides coupled to nitric oxide autoregulatory pathways with their strong influence on the brain centres controlling feelings of pleasure. During the phase of care of offspring, according to recent opinion, the influence of the peptides oxytocin and vasopressin are dominant.

One of the first hypotheses concerning the biological and endocrine basis of love was based on the view of the similar structure of catecholamine transmitters and amphetamines, which could cause a variety of effects similar to the starting stages of romantic love. In its first phase, romantic love has more a character of excitation and stress. There is a large body of evidence that stressful situations ease the formation of both new social bonds and intimate relationships in people and animals [17, 18]. The euphoria during the process of falling in love would then understandably be due to the fact that the dominant hormones are of adrenal origin: dopamine, noradrenalin and especially phenylethylamine. Catecholamines, seem possibly to be more related to psychological discomfort, as demonstrated by their higher levels in men and women when divorcing, during marital quarrels, and so on. In such stressful situations, not only are adrenalin levels raised, but also ACTH levels increase [2]. Attention has been given to the biogenic amines – mostly connected to the initial phases of love – which are somewhat similar in effect to amphetamines. Amphetamines show typical characteristics of addictive drugs and falling in love can truly be a certain form of addiction [19, 20]. Here should be mentioned that derivatives of amphetamine include such well-known psychostimulants with hallucinogenic properties drugs as 3,4-methylenedioxymethamphetamine (MDMA; ecstasy, "Adam") or the "love drug" (3,4-methylenedioxyethamphetamine, MDE, "Eve") and 3,4-methylenedioxyamphetamine (MDA "Love") [21, 22].

β-Phenylethylamine, together with tyramine, tryptamine and octopamine belong to the biogenic amines, which are found in trace amounts in the nervous system and bind to a specific family of receptors bound with the G-protein (GPCR). Neither their origin nor function in the nervous system is well known. β-Phenylethylamine and its metabolites (phenylethanolamine, tyramine, acetyl-phenylethylamine and phenylacetaldehyde) act on the dopamine system in certain areas of the brain, especially in the nigrostriate. The behaviour of animals has been monitored in experiments after i.v. injection of amines into the brain and

it was found that β-phenylethylamine and acetyl-phenylethylamine induced ipsilateral rotation (rotation on the same side, into which the substance had been injected). This certainly has nothing to do with the fact that love can cause heads to turn, but it does demonstrate the strong effect that these substances have on the central brain system. It is a psychomotor stimulating bioamine which acts on the acetylcholine system in striate and inhibits dopaminergic activity via the dopamine D(2) receptor.

No evidence has been presented that would support the theory concerning the effect of phenylethylamine in the phenomenon of being in love [23]. It was proved, however, that romantic love is associated with lower levels of platelet serotonin transporter, similarly to some psychoses [1] and pathological jealousy [24], and being in love is also accompanied with a significant increase of nerve growth factor, NGF [12] This neurotrophin even has a positive correlation with the intensity of the romantic love. Its levels gradually normalized after 12–24 months, as the romantic love changed to a stable state or faded, and were no longer different from those of control groups. In this relation it is even more interesting that levels of some neurotrophines, including NGF, were increased by kissing and this has been shown to lead to an improvement of allergic skin reactions [25].

Similar procedure as was used by the authors studying neurotropines was also used by the group of Marazziti. They not only compared normal pairs in love but also followed these pairs over a period of more than a year, when the love would no longer be a romantic one. They found higher cortisol levels and lower FSH levels in pairs, which were in love. They also found lower testosterone in men in love [3], which confirms the evidence of love being a stress condition. Also other studies [26] show that men who are romantically involved (i.e., are paired) have lower testosterone than single men, which may be due to a facultative adjustment of testosterone levels that respond to lower demands in mating effort. Increase of cortisol and decrease of FSH and testosterone are typical endocrine changes in stress situations. Not only being in love, but also separation from a close partner leads to a stress reaction in the hypothalamus-pituitary-adrenal system [27]. Previous research has shown that being partnered is associated with lower testosterone in men. To address how multiple partners may be associated with testosterone levels, the study of van Anders [49] examined men and women who were single, monoamorously partnered (partnered) or polyamorous (having multiple committed relationships). Men who were partnered had lower testosterone than all other men, and polyamorous men had higher testosterone than single men. Polyamorous women had higher testosterone than all other women.

According to the hypothesis of Shoja et al. [28] products of pineal gland melatonin and vasotocin might be the factors attenuating the romantic love.

Making social bonds enables to keep a physiological state of lower anxiety and reduced negative feelings [29, 30, 31]. In reality, most people in love in the early

phases of excitation and euphoria enter a stage in which there is a pronounced feeling of safety, calm and balance, which is controlled by a different type of hormone. The influence of endorphins may dominate in the later phase of love [32, 20]. Endorphins are substances whose effect is realized via the same receptors as those, which respond to exogenous opiates. Unlike amphetamine derivatives, endorphins are not produced in the adrenal gland but largely in the brain, and they do not excite but instead calm and dampen feelings of pain. There are also several neuroactive steroids, which are active in this phase of love. Neuroactive steroids modulate the excitatory effect of GABA receptors and have analgesic, anxiolytic, antidepressive and sedative effects.

Another hormone, which is definitely already known to belong to the regulation of biological reproduction, is oxytocin. The domain of its effect reaches through two of the phases of love. It is produced by the hypothalamus and released from neurohypophyseal terminals into the blood. It is produced also within defined brain regions that regulate emotional, cognitive, and social behaviours [33]. Doctors tend to think about oxytocin in relation to women more than to men due to hormone's effects on uterine contractions and milk ejection. Oxytocin also has an important role as a regulator of sexual and maternal behaviour or given positive social contact, in the reduction of stress. [9, 34, 35, 36, 37]. It possibly also affects mothers, so that they will fondle and care their children and most likely also has a similar effect on such activity between men and women. In the study of Gonzaga et al. [38] the nonverbal display of romantic love was related to the release of oxytocin. Increased oxytocin release is a part of the biological process of orgasm: in men and even stronger in women oxytocin levels increase at orgasm and following sexual climax decrease again [39]. Its levels increase during physical contact [40]. Mutual caressing leads to an inhibition of adrenergic activity caused by oxytocin, including lower blood pressure, especially in women. Oxytocin, secreted by the neurohypophysis, also causes a free feeling of satisfaction and affection and evidently has an anti-stress effect [37, 41] and according to recent findings, oxytocin also increases mutual trust between people [42], and has therefore come to be known as the "hormone of trust".

Oxytocin levels in men and women are similar and oxytocin receptors can be found in many tissues, especially nerve tissue, in both sexes. Oxytocin has been labelled as the "trust hormone" because extensive findings have shown that significant differences in the oxytocin receptors can be found between closely related types of voles, one of which (Microtus ochrogaster) is monogamous and which lives in a large social structure, whereas other types (Microtus pennsylvanicus a M. monatnus) are polygamous and lead solitary lives [43, 44]. The concentration of oxytocin receptors in the brain of monogamous voles is higher than of polygamous and also the localisation of oxytocin receptors differs among the species. The monogamous behaviour and the tendency to care for offspring in males can be stopped with injection of a drug antagonistic to oxytocin, atosiban or

barusiban, used as a tocolytic. On the other hand, monogamous behaviour is strengthened via dopamine D2 receptor, but not the D1 receptor.

Kosefeld et al [42] demonstrated that intranasal administration of oxytocin, a neuropeptide that plays a key role in social attachment and affiliation in non-human mammals, causes a substantial increase in trust among humans, thereby greatly increasing the benefits from social interactions.

In neurobiology of social bonds – partnership, courtship, faithfulness, care for offspring, relationships with other individuals – the neuropeptide oxytocin and vasopressin play an important role [45, 46]. These "hormones of love and fear" modulate the integration of information in the amygdala [47]. Vasopressin and oxytocin modulate the excitatory inputs into the central nucleus of amygdala in opposite manners [47].

Even if it may seem that science has extensive knowledge about the explanation of feelings in the various stages of love and how to measure their importance in the conception and upbringing of human offspring, it still remains a mystery as to how these events are initiated by that one partner selected among thousands, as if something made a spark, in order to cause the release of the correct sequence of hormonal drugs and aphrodisiacs and why even the most carefully mixed hormone cocktails have been unable to create a drink of love, where there are as yet no annoying presumptions. In animals these biological effects can be facilitated by factors such as pheromones [48] and other scents, however, in human marriage rituals and courting schemes these signal do not play a (major) role, which is evidenced by the fact that the vomeronasal organ in humans is, to a large extent, quite rudimentary compared to other mammals.

Our present knowledge on the contribution of hormones and endocrinology in the development of love is still limited. Perhaps in the future we will be able to create antihormones against disappointed love to prevent tragedies as suicides or it will be possible to apply a substance enhancing partner's faithfulness. However, I hope that love will, for a long time, stay an elixir mixed from both physical and spiritual ingredients, from both reality and imagination, from poetry and a fast-beating heart, even if there will always be a bit of a contribution from cortisol, endorphins and oxytocin.

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