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# The biochemistry of love: an oxytocin hypothesis

SSS Science and Society Series on Sex and Science

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Love is deeply biological. It pervades every aspect of our lives and has inspired countless works of art. Love also has a profound effect on our mental and physical state. A 'broken heart' or a failed relationship can have disastrous effects; bereavement disrupts human physiology and might even precipitate death. Without loving relationships, humans fail to flourish, even if all of their other basic needs are met.

As such, love is clearly not 'just' an emotion; it is a biological process that is both dynamic and bidirectional in several dimensions. Social interactions between individuals, for example, trigger cognitive and physiological processes that influence emotional and mental states. In turn, these changes influence future social interactions. Similarly, the maintenance of loving relationships requires constant feedback through sensory and cognitive systems; the body seeks love and responds constantly to interaction with loved ones or to the absence of such interaction.

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Although evidence exists for the healing power of love, it is only recently that science has turned its attention to providing a physiological explanation. The study of love, in this context, offers insight into many important topics including the biological basis of interpersonal relationships and why and how disruptions in social bonds have such pervasive consequences for behaviour and physiology. Some of the answers will be found in our growing knowledge of the neurobiological and endocrinological mechanisms of social behaviour and interpersonal engagement.

Nothing in biology makes sense except in the light of evolution. Theodosius Dobzhansky's famous dictum also holds true for explaining the evolution of love. Life on Earth is fundamentally social: the ability to interact dynamically with other living organisms to support mutual homeostasis, growth and reproduction evolved early. Social interactions are present in primitive invertebrates and even among prokaryotes: bacteria recognize and approach members of their own species. Bacteria also reproduce more successfully in the presence of their own kind and are able to form communities with physical and chemical characteristics that go far beyond the capabilities of the individual cell [1].

As another example, insect species have evolved particularly complex social systems, known as 'eusociality'. Characterized by a division of labour, eusociality seems to have evolved independently at least 11 times. Research in honey-bees indicates that a complex set of genes and their interactions regulate eusociality, and that these resulted from an "accelerated form of evolution" [2]. In other words, molecular mechanisms favouring high levels of sociality seem to be on an evolutionary fast track.

The evolutionary pathways that led from reptiles to mammals allowed the emergence of the unique anatomical systems and biochemical mechanisms that enable social engagement and selectively reciprocal sociality. Reptiles show minimal parental investment in offspring and form non-selective relationships between individuals. Pet owners might become emotionally attached to their turtle or snake, but this relationship is not reciprocal. By contrast, many mammals show intense parental investment in offspring and form lasting bonds with the offspring. Several mammalian species—including humans, wolves and prairie voles—also develop long-lasting, reciprocal and selective relationships between adults, with several features of what humans experience as 'love'. In turn, these reciprocal interactions trigger dynamic feedback mechanisms that foster growth and health.

Of course, human love is more complex than simple feedback mechanisms. Love might create its own reality. The biology of love originates in the primitive parts of the brain—the emotional core of the human nervous system—that evolved long before the cerebral cortex. The brain of a human 'in love' is flooded with sensations, often transmitted by the vagus nerve, creating much of what we experience as emotion. The modern cortex struggles to interpret the primal messages of love, and weaves a narrative around incoming visceral experiences, potentially reacting to that narrative rather than reality.

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Sex is the greatest invention of all time: not only has sexual reproduction facilitated the evolution of higher life forms, it has had a profound influence on human history, culture and society. This series explores our attempts to understand the influence of sex in the natural world, and the biological, medical and cultural aspects of sexual reproduction, gender and sexual pleasure.

It also is helpful to realize that mammalian social behaviour is supported by biological components that were repurposed or co-opted over the course of mammalian evolution, eventually allowing lasting relationships between adults. One element that repeatedly features in the biochemistry of love is the neuropeptide oxytocin. In large mammals, oxytocin adopts a central role in reproduction by helping to expel the big-brained baby from the uterus, ejecting milk and sealing a selective and lasting bond between mother and offspring [3]. Mammalian offspring crucially depend on their mother's milk for some time after birth. Human mothers also form a strong and lasting bond with their newborns immediately after birth, in a time period that is essential for the nourishment and survival of the baby. However, women who give birth by caesarean section without going through labour, or who opt not to breast-feed, still form a strong emotional bond with their children. Furthermore, fathers, grandparents and adoptive parents also form lifelong attachments to children. Preliminary evidence suggests that simply the presence of an infant releases oxytocin in adults [4,5]. The baby virtually 'forces' us to love it (Fig 1).

Emotional bonds can also form during periods of extreme duress, especially when the survival of one individual depends on the presence and support of another. There is also evidence that oxytocin is released in response to acutely stressful experiences, possibly serving as hormonal 'insurance' against overwhelming stress. Oxytocin might help to assure that parents and others will engage with and care for infants, to stabilize loving relationships and to ensure that, in times of need, we will seek and receive support from others.

The case for a major role for oxytocin in love is strong, but until recently has been based largely on extrapolation from research on parental behaviour [4] or social behaviours in animals [5,6]. However, human experiments have shown that intranasal delivery of oxytocin can facilitate social behaviours, including eye contact and social cognition [7]—behaviours that are at the heart of love.

Of course, oxytocin is not the molecular equivalent of love. It is just one important component of a complex neurochemical system that allows the body to adapt to highly emotive situations. The systems necessary for reciprocal social interactions involve extensive neural networks through the brain and autonomic nervous system that are dynamic and constantly changing during the lifespan of an individual. We also know that the properties of oxytocin are not predetermined or fixed. Oxytocin's cellular receptors are regulated by other hormones and epigenetic factors. These receptors change and adapt on the basis of life experiences. Both oxytocin and the experience of love change over time. In spite of limitations, new knowledge of the properties of oxytocin has proven useful in explaining several enigmatic features of love.

To dissect the anatomy and chemistry of love, scientists needed a biological equivalent of the Rosetta stone. Just as the actual stone helped linguists to decipher an archaic language by comparison to a known one, animal models are helping biologists draw parallels between ancient physiology and contemporary behaviours. Studies of socially monogamous mammals that form long-lasting social bonds, such as prairie voles, are helping scientists to understand the biology of human social behaviour.

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Research in voles indicates that, as in humans, oxytocin has a major role in social interactions and parental behaviour [5,6,8]. Of course, oxytocin does not act alone. Its release and actions depend on many other neurochemicals, including endogenous opioids and dopamine [9]. Particularly important to social bonding are the interactions between oxytocin and a related peptide, vasopressin. The systems regulated by oxytocin and vasopressin are sometimes redundant. Both peptides are implicated in behaviours that require social engagement by either males or females, such as huddling over an infant [5]. It was necessary in voles, for example, to block both oxytocin and vasopressin receptors to induce a significant reduction in social engagement either among adults or between adults and infants. Blocking only one of these two receptors did not eliminate social approach or contact. However, antagonists for either the oxytocin or vasopressin receptor inhibited the selective sociality, which is essential for the expression of a social bond [10,11]. If we accept selective social bonds, parenting and mate protection as proxies for love in humans, research in animals supports the hypothesis that oxytocin and vasopressin interact to allow the dynamic behavioural states and behaviours necessary for love.

Oxytocin and vasopressin have shared functions, but they are not identical in their actions. The specific behavioural roles of oxytocin and vasopressin are especially difficult to untangle because they are components of an integrated neural network with many points of intersection. Moreover, the genes that regulate the production of oxytocin and vasopressin are located on the same chromosome, possibly allowing a coordinated synthesis or release of these peptides. Both peptides can bind to, and have, antagonist or agonist effects on each other's receptors. Furthermore, the pathways necessary for reciprocal social behaviour are constantly adapting: these peptides and the systems that they regulate are always in flux.

In spite of these difficulties, some of the functions of oxytocin and vasopressin have been identified. Vasopressin is associated with physical and emotional mobilization, and supports vigilance and behaviours needed for guarding a partner or territory [6], as well as other forms of adaptive self-defence [12]. Vasopressin might also protect against 'shutting down' physiologically in the face of danger. In many mammalian species, mothers behave agonistically in defence of their young, possibly through the interactive actions of vasopressin and oxytocin [13]. Before mating, prairie voles are generally social, even towards strangers. However, within approximately one day of mating, they begin to show high levels of aggression towards intruders [14], possibly serving to protect or guard a mate, family or territory. This mating-induced aggression is especially obvious in males.

By contrast, oxytocin is associated with immobility without fear. This includes relaxed physiological states and postures that allow birth, lactation and consensual sexual behaviour. Although not essential for parenting, the increase of oxytocin associated with birth and lactation might make it easier for a woman to be less anxious around her newborn and to experience and express loving feelings for her child [15]. In highly social species such as prairie voles, and presumably in humans, the intricate molecular dances of oxytocin and vasopressin

**Fig 1** | As a one-year-old Mandrill infant solicits attention, she gains eye contact with her mother. © 2012 Jessie Williams.

fine-tune the coexistence of care-taking and protective aggression.

The biology of fatherhood is less well studied. However, male care of offspring also seems to rely on both oxytocin and vasopressin [5]; even sexually naive male prairie voles show spontaneous parental behaviour in the presence of an infant [14]. However, the stimuli from infants or the nature of the social interactions that release oxytocin and vasopressin might differ between the sexes [4].

Parental care and support in a safe environment are particularly important for mental health in social mammals, including humans and prairie voles. Studies of rodents and lactating women suggest that oxytocin has the capacity to modulate the behavioural and autonomic distress that typically follows separation from a mother, child or partner, reducing defensive behaviours and thereby supporting growth and health [6].

During early life in particular, trauma or neglect might produce behaviours and emotional states in humans that are socially pathological. As the processes involved in creating social behaviours and social emotions are delicately balanced, they might be triggered in inappropriate contexts, leading to aggression towards friends or family. Alternatively, bonds might be formed with prospective partners who fail to provide social support or protection.

Males seem to be especially vulnerable to the negative effects of early experiences, possibly explaining their increased sensitivity to developmental disorders. Autism spectrum disorders, for example, defined in part by atypical social behaviours, are estimated to be three to ten times more common in males than females. The implication of sex differences in the nervous system, and in response to stressful experiences for social behaviour, is only slowly becoming apparent [8]. Both males and females produce vasopressin and oxytocin and are capable of responding to both hormones. However, in brain regions that are involved in defensive aggression, such as the extended amygdala and lateral septum, the production of vasopressin is androgen-dependent. Thus, in the face of a threat, males might experience higher central levels of vasopressin.

> **In highly social species […] the intricate molecular dances of oxytocin and vasopressin fine-tune the coexistence of care-taking and protective aggression**

Oxytocin and vasopressin pathways, including the peptides and their receptors, are regulated by coordinated genetic, hormonal and epigenetic factors that influence the adaptive and behavioural functions of these peptides across the animal's lifespan.

As a result, the endocrine and behavioural consequences of stress or a challenge might be different for males and females [16]. When unpaired prairie voles were exposed to an intense but brief stressor, such as a few minutes of swimming or injection of the adrenal hormone corticosterone, the males (but not females) quickly formed new pair bonds. These and other experiments suggest that males and females have different coping strategies, and possibly experience both stressful experiences and even love in ways that are gender-specific.

Love is an epigenetic phenomenon: social behaviours, emotional attachment to others and long-lasting reciprocal relationships are plastic and adaptive and so is the biology on which they are based. Because of this and the influence on parental behaviour and physiology, the impact of an early experience can pass to the next generation [17]. Infants of traumatized or highly stressed parents might be chronically exposed to vasopressin, either through their own increased production of the peptide, or through higher levels of vasopressin in maternal milk. Such increased exposure could sensitize the infant to defensive behaviours or create a life-long tendency to overreact to threat. On the basis of research in rats, it seems, that in response to adverse early experiences or chronic isolation, the genes for vasopressin receptors can become upregulated [18], leading to an increased sensitivity to acute stressors or anxiety that might persist throughout life.

**…oxytocin exposure early in life not only regulates our ability to love and form social bonds, it also has an impact on our health and well-being**

Epigenetic programming triggered by early life experiences is adaptive in allowing neuroendocrine systems to project and plan for future behavioural demands. However, epigenetic changes that are long-lasting can also create atypical social or emotional behaviours [17] that might be more likely to surface in later life, and in the face of social or emotional challenges. Exposure to exogenous hormones in early life might also be epigenetic. Prairie voles, for example, treated with vasopressin post-natally were more aggressive later in life, whereas those exposed to a vasopressin antagonist showed less aggression in adulthood. Conversely, the exposure of infants to slightly increased levels of oxytocin during development increased the tendency to show a pair bond in voles. However, these studies also showed that a single exposure to a higher level of oxytocin in early life could disrupt the later capacity to pair bond [8]. There is little doubt that either early social experiences or the effects of developmental exposure to these neuropeptides can potentially have long-lasting effects on behaviour. Both parental care and exposure to oxytocin in early life can permanently modify hormonal systems, altering the capacity to form relationships and influence the expression of love across the lifespan. Our preliminary findings in voles suggest further that early life experience affects the methylation of the oxytocin receptor gene and its expression [19]. Thus, we can plausibly argue that "love is epigenetic."

Given the power of positive social experiences, it is not surprising that a lack of social relationships might also lead to alterations in behaviour and concurrently changes in oxytocin and vasopressin pathways. We have found that social isolation reduced the expression of the gene for the oxytocin receptor, and at the same time increased the expression of genes for the vasopressin peptide (H.P. Nazarloo and C.S. Carter, unpublished data). In female prairie voles, isolation was also accompanied by an increase in blood levels of oxytocin, possibly as a coping mechanism. However, over time, isolated prairie voles of both sexes showed increases in measures of depression, anxiety and physiological arousal, and these changes were seen even when endogenous oxytocin was elevated. Thus, even the hormonal insurance provided by endogenous oxytocin in the face of the chronic stress of isolation was not sufficient to dampen the consequences of living alone. Predictably, when isolated voles were given additional exogenous oxytocin this treatment restored many of these functions to normal [20].

On the basis of such encouraging findings, dozens of ongoing clinical trials are attempting to examine the therapeutic potential of oxytocin in disorders ranging from autism to heart disease (Clinicaltrials.gov). Of course, as in voles, the effects are likely to depend on the history of the individual and the context, and to be dose-dependent. With power comes responsibility, and the power of oxytocin needs to be respected.

Although research has only begun to examine the physiological effects of these peptides beyond social behaviour, there is a wealth of new evidence indicating that oxytocin influences physiological responses to stress and injury. Thus, oxytocin exposure early in life not only regulates our ability to love and form social bonds, it also has an impact on our health and well-being. Oxytocin modulates the hypothalamic–pituitary adrenal (HPA) axis, especially in response to disruptions in homeostasis [6], and coordinates demands on the immune system and energy balance. Long-term secure relationships provide emotional support and downregulate reactivity of the HPA axis, whereas intense stressors, including birth, trigger activation of the HPA axis and sympathetic nervous system. The ability of oxytocin to regulate these systems probably explains the exceptional capacity of most women to cope with the challenges of child-birth and child-rearing. The same molecules that allow us to give and receive love, also link our need for others with health and well-being.

**The protective effects of positive sociality seem to rely on the same cocktail of hormones that carry a biological message of 'love' throughout the body**

Of course, love is not without danger. The behaviours and strong emotions triggered by love might leave us vulnerable. Failed relationships can have devastating, even deadly, effects. In 'modern' societies humans can survive, at least after childhood, with little or no human contact. Communication technology, social media, electronic parenting and many other technological advances of the past century might place both children and adults at risk for social isolation and disorders of the autonomic nervous system, including deficits in their capacity for social engagement and love [21].

Social engagement actually helps us to cope with stress. The same hormones and areas of the brain that increase the capacity of the body to survive stress also enable us to better adapt to an ever-changing social and physical environment. Individuals with strong emotional support

and relationships are more resilient in the face of stressors than those who feel isolated or lonely. Lesions in bodily tissues, including the brain, heal more quickly in animals that are living socially compared with those in isolation [22]. The protective effects of positive sociality seem to rely on the same cocktail of hormones that carry a biological message of 'love' throughout the body.

As only one example, the molecules associated with love have restorative properties, including the ability to literally heal a 'broken heart'. Oxytocin receptors are expressed in the heart, and precursors for oxytocin seem to be crucial for the development of the fetal heart [23]. Oxytocin exerts protective and restorative effects in part through its capacity to convert undifferentiated stem cells into cardiomyocytes. Oxytocin can facilitate adult neurogenesis and tissue repair, especially after a stressful experience. We know that oxytocin has direct anti-inflammatory and anti-oxidant properties in *in vitro* models of atherosclerosis [24]. The heart seems to rely on oxytocin as part of a normal process of protection and self-healing.

A life without love is not a life fully lived. Although research into mechanisms through which love protects us against stress and disease is in its infancy, this knowledge will ultimately increase our understanding of the way that our emotions have an impact on health and disease. We have much to learn about love and much to learn from love.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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