Review Article

The orgasmic history of oxytocin: Love, lust, and labor

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ABSTRACT

Oxytocin has been best known for its roles in female reproduction. It is released in large amounts during labor, and after stimulation of the nipples. It is a facilitator for childbirth and breastfeeding. However, recent studies have begun to investigate oxytocin's role in various behaviors, including orgasm, social recognition, bonding, and maternal behaviors. This small nine amino acid peptide is now believed to be involved in a wide variety of physiological and pathological functions such as sexual activity, penile erection, ejaculation, pregnancy, uterine contraction, milk ejection, maternal behavior, social bonding, stress and probably many more, which makes oxytocin and its receptor potential candidates as targets for drug therapy. From an innocuous agent as an aid in labor and delivery, oxytocin has come a long way in being touted as the latest party drug. The hormone of labor during the course of the last 100 years has had multiple orgasms to be the hormone of love. Many more shall be seen in the times to come!

Key words: Endocrinology, history, labor, love, obstetrics, oxytocin, pitocin

Introduction

Traditionally, it has been artists, poets, and playwrights who have made the greatest progress in humanity's understanding of love. However, recently endocrinologists, who were never considered very romantic, have challenged this notion, and now rather have a lot to say about how and why people love each other. Research is also shedding light on some of the more extreme forms of sexual behavior. And, controversially, some endocrine scientists see hormonal manipulation as the doorway to a future where love is guaranteed, because it will be provided chemically, or even genetically engineered from conception.

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Comparative Endocrinology

The scientific tale of love begins innocently enough with voles. The prairie vole is a sociable rodent, found in the woodlands of Europe and Asia, one of the only 3% of mammal species that appear to form monogamous relationships. Mating between prairie voles is a tremendous effort which takes almost 24 h, following which they bond for life. They prefer to spend time with each other, groom each other for hours and at end, nest together. They avoid meeting other potential mates.

However, another vole, a close relative called the montane vole, has no interest in partnership beyond one-night-stand sex. What is intriguing is that this major difference in behavior in two vole species, which are more than 99% genetically alike, is just because of a handful of genes, which affect their endocrine function.

The details of the vole story are fascinating. When prairie voles have sex, two posterior pituitary hormones, oxytocin and vasopressin, are released. If the release of these hormones is blocked, prairie-voles' sex becomes a fleeting

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affair, similar to that normally enjoyed by their montane cousins. Conversely, if prairie voles are given an injection of the hormones, but prevented from having sex, they will still form a preference for their chosen partner.

Does this mean that an injection of oxytocin can make prairie voles fall in love? Or that it encourages monogamy? A clue to what is happening, and how these results might bear on human behavior, was found when oxytocin was administered to the montane vole. It was found to make no difference. It turned out that the monogamous prairie vole has receptors for oxytocin and vasopressin in brain regions associated with reward and reinforcement, whereas the philandering montane vole does not.

The million rupee question: do humans have brains similar to prairie voles? Interestingly, there is no research to establish whether humans make a part of the faithful 3% category of mammals which prairie voles belong to, and which exhibit fidelity to partners.

Endocrine Contribution

So, what have reproductive endocrinologists contributed to the demystification and understanding of love and lust? They found that the oxytocin: the hormone of labor is also the hormone of love. It took no time for oxytocin to acquire fancy names such as "the bonding hormone," "the cuddle hormone" and even "the love hormone." And giving meaning to its new founded names, it generated the lust for money and resulted in products like "trust elixir," an oxytocin-laced perfume being made available in many parts of the world [http://www.verolabs.com/]. However, concerns were raised that the oxytocin should not be abused as a recreational drug such as "ecstacy." This was because oxytocin is not unlike the drug ecstasy, which triggers the release of serotonin, dopamine and oxytocin in the brain and heightens users' feelings of trust and intimacy, even among complete strangers. Fortunately, the concerns seem unfounded given that the hormone does not produce a "high" as do other drugs of abuse.

In this review, we shall trace the orgasmic history of oxytocin, from the days of its birth to its present day status, and take a look into its future.

Early History

It was in 1895 that Oliver and Schäfer discovered the first biological effect of the pituitary gland.[1] They found that the extracts of the pituitary when injected into mammals raised their blood pressure---the pressor effect. Howell showed a few years later that this activity resided in the posterior lobe.[2] Since that time, other biological activities of posterior pituitary extracts were noted, particularly the uterine-contracting or oxytocic effect by Dale in 1906;[3] the milk-ejecting effect by Ott and Scott in 1910;[4] the blood-pressure-lowering effect in birds, the so-called avian depressor effect by Paton and Watson in 1912;[5] and the inhibition of urine excretion in man, the antidiuretic effect by Von den Velden in 1913.[6] It was indeed initially thought that oxytocin was devoid of pressor and antidiuretic activity. However, it was later found out that both the pressor and antidiuretic activity, were inherent properties of the oxytocin molecule.[7]

In 1906, Sir Henry Dale found that extracts from the human posterior pituitary gland contracted the uterus of a pregnant cat.[3] He coined the name oxytocin from the Greek words *ωκυξ*, *τοκοξ*, meaning "swift birth." Sir Henry Dale also worked on histamine and acetylcholine among others and was jointly awarded the Nobel Prize in 1936 "for discoveries relating to chemical transmission of nerve impulses." Forty seven years after Dale discovered it, oxytocin, a nine amino acid CNS neuropeptide, was the first ever polypeptide hormone to be sequenced and synthesized. It was done by Vincent du Vigneaud and for this achievement he was awarded the Nobel Prize in 1955.[8]

Few people would know that the works of Vincent du Vigneaud on oxytocin were a result of his original interest in insulin. At no less an occasion than the Nobel Lecture which Vigneaud delivered on the 12th day of December in 1955, he brought out that oxytocin was a result of a "trail of sulfa research." Vincent du Vigneaud described oxytocin as the principal uterine-contracting and milk-ejecting hormone of the posterior pituitary gland. Its synthesis was the culmination of a trail of research stemming from his original interest in sulfur and in insulin, a sulfur-containing compound.

It was enthusiasm of Professor H.B. Lewis in sulfur at the University of Illinois that aroused the interest of Vigneaud in the biochemistry of sulfur compounds. In 1923, W. C. Rose who succeeded Lewis as professor of biochemistry at Illinois, gave an account of the exciting discovery of insulin by Banting and Best, in a lecture he delivered on his return from a meeting in Toronto. This initiated Vigneaud's interest in insulin. Interestingly, at that time it was not even thought of that insulin would eventually turn out to be a sulfur-containing compound. However, interest in diabetes lead to the study of the structure of insulin which finally directed to work on the posterior pituitary hormones. Oxytocin was isolated from lyophilized posterior lobes of beef pituitary glands.[9]

This discovery culminated in 1952 in the isolation of a crystalline flavianate of oxytocin with Pierce,[10] the first crystalline derivative of this hormone to be isolated. It is of interest that an oxytocic fraction was also obtained from hog posterior pituitary glands which had a distribution curve approximately the same as that from the beef glands.[10] In addition, the oxytocin obtained from the hog pituitary had the same amino acid composition and potency as that obtained from beef. The synthetic product was found fully effective in stimulating labor in full term women, and in milk ejection, and could not be distinguished from the natural oxytocin in its action. Approximately 1 μg of either the natural oxytocin or the synthetic material given intravenously to recently parturient women induced milk ejection in 20-30 s.[11]

Current Concepts

Oxytocin has been best known for its roles in female reproduction. It is released in large amounts during labor, and after stimulation of the nipples. It is a facilitator for childbirth and breastfeeding. One of the oldest applications of oxytocin as a proper drug is as a therapeutic agent during labor and delivery. It is a stimulant widely employed to induce or augment labor, especially at term, when adequate oxytocin receptors are present. It is also one of the principal uterotonic drug used to prevent post partum hemorrhage.

However, recent studies have begun to investigate oxytocin's role in various behaviors, including orgasm, social recognition, bonding, and maternal behavior. For this reason, it is now sometimes referred to as the "love hormone" and many such names described earlier.

Social bonding is essential to species survival since it favors reproduction, protection against predators and environmental changes, and furthers brain development.[12] Exclusion from the group results in individual physical and mental disorders and leads ultimately to death, both in animal models and in primitive human tribes.[13] Oxytocin and its receptors appear to hold the leading position among the candidates for the substance of "happiness." If not "happiness," at least it now seems to be an important brain compound in building trust, which is necessary in developing emotional relationships, a process also referred to as social bonding. A recent study by Kosfeld published in *Nature* has demonstrated that in people playing a money game, a nasal spray of oxytocin raised their trust, even in a stranger.[14] Such findings do bring some hope in the treatment of social disorders such as phobia.[15] Furthermore, oxytocin and its receptors have been found to be involved in a plethora of social and affective, physiological and pathophysiological behaviors, ranging from attachment security, mating, paternal behavior and motherhood to autism and obsessive–compulsive disorder.[12,16-20] Indeed, in the Prairie voles, oxytocin released into the brain of the female during sexual activity is important for forming a monogamous pair bond with her sexual partner. Vasopressin appears to have a similar effect in males.[21] Plasma concentrations of oxytocin have been reported to be higher amongst people who claim to be falling in love. Oxytocin injected into the cerebrospinal fluid causes spontaneous penile erections in rats[22] reflecting actions in the hypothalamus and spinal cord. It shows that the "love hormone" can have a role to cause erection during sexual arousal. Arletti and Pedersen separately studied that oxytocin increases sexual receptivity and can counteract impotence.[23] This "cuddle drug" can indeed make partners cuddle up, and can have a larger role in treatment for infertility in future! Can it indeed increase the lust for love? Interestingly, at least two studies have found increases in plasma oxytocin at orgasm---in both men and women.[24,25]

Oxytocin is responsible for bringing in what is specifically called as "maternal behavior." If oxytocin antagonists are given to sheep and rat females after parturition, they do not exhibit typical maternal behavior. By contrast, virgin female sheep shows maternal behavior toward foreign lambs upon cerebrospinal fluid infusion of oxytocin, which they would not do otherwise.[26]

Many studies done in the past 15 years have tried to study the relationship between autism and oxytocin. In 1998, Modahl *et al.*, in their study found significantly lower levels of oxytocin in blood plasma of autistic children.[27] Five years later, in 2003, Hollander and associates found a decrease in autism spectrum repetitive behaviors when oxytocin was administered intravenously.[28] Further in 2007, in another study Hollander *et al.*, reported that oxytocin helped autistic adults retain the ability to evaluate the emotional significance of speech intonation.[29] More work is definitely required to investigate the role of oxytocin in autism, but present work is definitely showing a ray of hope in finding a role for oxytocin in treatment of autism.

In addition to fundamental insights into the role of oxytocin in the CNS, an increasing number of studies performed recently have shown the importance of oxytocin and its involvement, directly or indirectly, in several pathophysiological disorders in the nervous system and other organs. Oxytocin has been broadly discussed under the following titles: "oxytocin and addiction"; "oxytocin increases trust in humans"; "oxytocin increases generosity in humans"; "search for autism treatments turns to 'trust

hormone"'; "being human: love: neuroscience reveals all"; "oxytocin: the great facilitator of life".[30-34]

Oxytocin does reduce cravings. Kovacs in a study demonstrated that when oxytocin was administered to rodents who were addicted to cocaine, morphine or heroin; the rats opted for less drugs or showed fewer symptoms of withdrawal.[35] Billings recently reported that oxytocin also reduces cravings for sweets. This way, can it emerge as a weight reducing and deaddiction agent? Oxytocin is calming. Even a single rat injected with oxytocin has a calming effect on a cage full of anxious rats.[23] Can it be a silver streak in treatment of anxiety disorders!

Oxytocin has been found to act in pathologic processes far removed from reproduction and nervous system as well. Links have been made between oxytocin administration and injury healing. Vitalo *et al.*, provide evidence that oxytocin injections had a positive influence on wound healing in isolated reared rats.[36] Legros also has reported that oxytocin counteracts the effects of cortisol, the stress hormone.[37] Less stress means increased immunity and faster recovery. This may open up vistas for the use of this hormone in chronic ulcers.

Oxytocin secreted from the pituitary gland cannot re-enter the brain because of the blood-brain barrier. Instead, the behavioral effects of oxytocin are thought to reflect release from centrally projecting oxytocin neurons, different from those that project to the pituitary gland. Oxytocin receptors are expressed by neurons in many parts of the brain and spinal cord, including the amygdala, ventromedial hypothalamus, septum and brainstem. Peripheral, hormonal actions of oxytocin are mediated by specific, high affinity oxytocin receptors. The peripheral actions of oxytocin mainly reflect secretion from the pituitary gland. The letdown reflex and the uterine contractions are both affected this way only. Due to its similarity to vasopressin, oxytocin can reduce the excretion of urine slightly. More important, in several species, oxytocin can stimulate sodium excretion from the kidneys, and in humans, high doses of oxytocin can result in hyponatremia.

The Potential

Therefore, the potential of oxytocin for drug targeting is immense. While it brings some hope for alleviating serious social disorders, the issue appears extremely complex to tackle, as the specificity of action might be difficult to control.[38] Oxytocin has become an interesting tool, especially through the design of oxytocin agonists and antagonists, and a potential candidate for drug research and therapeutics in humans.

One of the main and now well-characterized peripheral oxytocin targets is the erectile tissues, i.e., corpus spongiosum and corpus cavernosum. Though it appears to be an indirect effect, oxytocin injected in the rats induces penile erection.[39] Moreover, oxytocin is thought to be associated with ejaculation by increasing sperm number and contracting ejaculatory tissues especially prostatic urethra, bladder neck, and ejaculatory duct.[40] An interesting study has shown that oxytocin-stimulated ejaculation is specifically mediated by vasopressin V1a receptors; following which V1a antagonists have been proposed as a putative therapy for premature ejaculation.[41] Therefore, oxytocin may have a role to play in management of male infertility.

Another promising therapeutic breakthrough in the next years could be the development of oxytocin-based medications to treat altered nociception. At the peripheral level, oxytocin also seems to be a key component in bone formation, glycaemia, male sexuality, cardiac differentiation, and nonregulated cellular proliferation.

Conclusion

The story of oxytocin begins right before pregnancy, continues during birth and later, travels from the brain to the heart and throughout the entire body, triggering, or modulating a full range of physiological functions and emotions: happiness, attraction, love, affection, and hatred after stress. These are all governed directly or indirectly, at least in part, by oxytocin. The multidimensional nonapeptide appears to play a central role in social behavior, and emerging clinical trials seek to assess and define its therapeutic potential in the treatment of pathophysiological behaviors. Therefore, there is a strong impetus to develop and establish new technological tools that will enable us to harness the full potential of oxytocin and its congeners.

Taken together, the insights gained from more than 100 years of research indicate that the success story of the hormone of "swift birth" will continue unabated. The potential therapeutic uses for oxytocin and more long-acting and specific analogues of oxytocin are huge. Chemical, physiopathological, psychological, philosophical, and ethical studies will reinforce the development of new drugs involving the use of oxytocin, its agonists and antagonists for various human disorders such as autism, premature ejaculation, osteoporosis, diabetes and cancer.

From an innocuous agent as an aid in labor and delivery, to being touted as the latest party drug, oxytocin has come a long way. More research should be encouraged in this field in our country and across the world. Awareness should be generated about the exciting history of this hormone

among reproductive and medical endocrinologists, just as it is for insulin.

It seems that during the course of the last 100 years, the hormone of love has had multiple orgasms. It shall experience many more in the times to come. It has been documented that peak nocturnal uterine activity at the end of gestation is because of the nocturnal peak in plasma concentrations of oxytocin.[42] But is it also true that this nocturnal peak of oxytocin is responsible for other nocturnal stories which culminate, nine months later, in keeping the obstetricians awake at night? Much more work needs to be done to completely demystify the mystery of "oxytocin: the mystery hormone", a new name which can be added to the plethora of existing names this exciting hormone has already earned.

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