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EDITORIAL

Endorphins, oxytocin, sexuality and romantic relationships: An understudied area

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Abstract

Endorphins are the body's natural opioids that are created and released by the central nervous system, hypothalamus and pituitary gland. Endorphins have a reputation for pain reduction, enhancing excitement or satisfaction, boosting confidence, enabling control of emotions and generating feelings of euphoria, and are involved in the natural reward cycle. There is also evidence in the literature suggesting the role of endorphins in sexuality (including sexual function and sexual behaviours), as they may regulate the release of sex hormones, prolactin and growth hormone, which are involved in sexual function and love. Endogenous oxytocin is another intrinsic hormone whose role in inducing labour contractions, the delivery of the baby and stimulating lactation has been well studied. However, the potential impact of endorphins and oxytocin on sexuality and romantic relationships is not well understood. This article reviews the research on endorphins and endogenous oxytocin and how they relate to human sexuality and romantic relationships. Some animal studies report the effect of endorphin and oxytocin on sex hormones and mating behaviours, but these findings have not been supported by research into human behaviour, indicating many gaps in knowledge relating to the association between these hormones and human sexuality.

Key words: Romantic relationship; Sexual behaviour; Sexual function; Endorphins; Oxytocin; Sexuality

Core tip: Less is known about the association between endogenous opioids and sexual function and behaviors in

humans. There are mixed reports regarding the impact of oxytocin on sexuality and romantic relationships. The importance of physiological changes during sexual activity and how they can affect human relationships and the gaps in the literature highlight the need for high-quality research to extend our understanding of the hormonal physiology of sexual function and the role of endorphins and oxytocin in human sexuality.

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INTRODUCTION

Endorphins are the body's natural opioids, or endogenous opioids, that are created and released by the central nervous system (CNS), hypothalamus and pituitary gland. Endorphins have a reputation for pain reduction, enhancing excitement or satisfaction, boosting confidence, enabling control of emotions and generating feelings of euphoria, and are involved in the natural reward cycle. The release of endorphins in the human body is triggered by a variety of factors, including massage and bodywork[1], exercise[2], active performance of music[3], consumption of certain foods such as dark chocolate[4], environmental factors such as ultraviolet light[5], and childbirth[6]. There is also evidence in the literature suggesting the role of endorphins in sexuality. It is suggested that endorphins regulate the release of other hormones, such as sex hormones, prolactin and growth hormone, which are involved in sexual function and love[7,8].

Endogenous oxytocin is another intrinsic hormone whose receptors were first discovered in 1984 because of their role in inducing labor contractions, the delivery of the baby and stimulating lactation. Endogenous oxytocin is primarily synthesised in the hypothalamus and is then stored in the posterior pituitary gland, from where it is released into the bloodstream[9]. The release of endogenous oxytocin can be provoked by a variety of stimuli including sexual and reproductive stimuli (copulation, genital and breast stimulation, birth, olfactory stimuli, and sucking)[10] and non-sexual stimuli (*i.e.,* grooming, massage and contact with offspring)[11].

The roles of endorphins and oxytocin are well researched and understood in some areas of health, but their potential impacts on sexuality and romantic relationships are only beginning to be understood. The purpose of this editorial is to review current understanding of endorphins and endogenous oxytocin and how they relate to human sexuality (including sexual function and sexual behaviours, for the purpose of this review).

EFFECT OF BETA-ENDORPHIN ON SEXUALITY AND ROMANTIC RELATIONSHIPS

Human studies

The association between beta-endorphin and sexuality and romantic relationships is mutual, with endogenous sex steroids affecting the neurobiology of sexual function by directly influencing receptors at the nuclear and membrane level or by indirectly affecting the neurotransmitters of neuropeptides (endogenous oxytocin and endorphins)[12]. For this reason, it has been suggested that endorphins may be involved in the regulation of sexual function in humans.

It has been suggested that a mild increase in the beta-endorphin level creates a sense of wellbeing, and that a greater increase may lead to analgesia and euphoria. A variety of behavioral experiences can activate the release of beta-endorphin. For example, exercise stimulates secretion of corticotropin-releasing hormone, resulting in an increase in ACTH and endorphins that may enhance an individual's sexuality[13]. In addition to aerobic exercise, discontinuation of tobacco use and illicit drug use and reduced alcohol consumption improve tissue oxygenation, promote metabolism, reduce body mass index and stimulate endorphin release that may, in turn, boost sexual response[14].

An increase of endorphin levels during sexual activity in humans is presumed to contribute to attachment and bonding between partners, similar to that of a mother and her newborn[8]. However, contradictory reports in the literature question the association between sexuality and endorphin levels. For example, in a small study on 10 healthy women, sexual arousal and orgasm resulted in a sharp increase in cardiovascular parameters and plasma catecholamine concentrations along with an increase in the concentration of plasma prolactin, but no changes were seen in the plasma concentrations of beta-endorphin[15]. A similar neuroendocrine response pattern to sexual arousal and orgasm in men was reported in an earlier study by Krüger *et al*[16]. Although they showed a transient increase in heart rate and blood pressure as well as noradrenaline and prolactin plasma levels, no changes were seen in the plasma beta-endorphin and other endocrine variables.

Less is known about the association between endogenous opioids and sexual function and behaviors in humans, but it is known that exogenous opiates negatively affect the sexuality of male and female who misuse opiate drugs and contribute to their reduced sexual desire, impaired sexual arousal, decreased genital response, delayed or blocked ejaculation, orgasm dysfunction and infertility[17]. Opiate drugs negatively affect sexual function through reducing the levels of sex hormones, and their effect on the endocrine system begins immediately after they are taken[18]. Although little is known about the exact mechanism of sexual

dysfunction in people who are opioid-addicted, and studies in this area are small, the available evidence shows a high prevalence of opioid-induced hypogonadism (up to 90%) in patients who take opiate drugs such as heroin[19], methadone[20], intrathecal opioids[21] and systemic (oral or transdermal) opioids[22,23]. According to a systematic review and meta-analysis[24] of the testosterone levels in men and women while using opiate drugs, regular use suppresses the testosterone level in men regardless of the type of opioid being ingested. Testosterone levels in women are not affected by opiate drugs. This sex difference suggests that opiate drugs may have differential mechanisms for endocrine disruption in men and women, and this should be taken into consideration when treating sexual problems in people who are opiate-dependent[24]. Since there may be different endocrine targets to aim for even in non-opioid-dependent men and women while trying to treat their sexual dysfunction using pharmaceutical drugs, any future drug development for sexual dysfunction needs to consider these differences.

The negative effects of opiate drugs on male sexual function are reversible after opiate withdrawal[25] or administration of opiate antagonists[26]. The positive effects of opiate antagonists are increased luteinizing hormone (LH) pulsatility, raised serum testosterone levels[27], increased *in vitro* sperm motility after administration of naloxone[28], recurrent spontaneous penile erections, frequent orgasms and more intense sexual arousal and orgasm in healthy adult men who were not addicted to opiates, after administration of naltrexone[29]. However, these findings are not supported by animal research, indicating a lack of substantial influence of acute or chronic naloxone administration on different sexual activities of isolated and group-housed male rats[30]. Details of other animal research are discussed in the next section.

The limited research in humans, especially in women, has created inconsistent but, in some cases, interesting results. For example, in the study by Goldstein and Hansteen[31], a single male subject was recruited and the researchers prematurely concluded that there is no evidence of the involvement of endorphins in male sexual arousal. Other research by Gillman and Lichtigfeld[32] found that administration of a 2 mg dose of naloxone on two separate occasions enhanced orgasm and pleasure in women, while a single 2 mg dose of naloxone inhibited arousal and orgasm for up to 10 min, suggesting that the relationship of naloxone to orgasm is dose-dependent and potentially parabolic. This is consistent with the notion that endogenous opiates, such as beta-endorphin, have both inhibitory and excitatory effects, but the explanation for the dose-response effect remains obscure[7].

Animal studies

Findings of animal studies suggest that opioid peptides may have both excitatory and inhibitory effects on sexual performance and behaviours[7,33]. When opioid peptides are released in response to stress, they impose their inhibitory effects by acting in the medial preoptic area and the paraventricular nucleus that, in turn, impairs sexual performance[34]. According to animal studies, it is suggested that endorphins regulate the release of other hormones, such as sex hormones, prolactin and growth hormone, that are involved in sexual function and attachment[7,8]. It has also been suggested that this may be relevant to the low level of sexual desire in people with symptoms of depression[35].

Preliminary studies have investigated the mechanisms of inhibition of sexual behavior by opioids. Myers and Baum[36] showed that naloxone, the opiate receptor antagonist, has a facilitatory effect on masculine sexual performance in rats, resulting in the release of gonadotropin releasing hormone (GnRH). A later study[37] indicated that infusion of opioid antagonists into the mesencephalic central gray matter increases neuronal GnRH output that in turn enhances the likelihood of lordosis behavior in estrogen-primed female rats. Other studies have shown that acute treatment with opioid antagonists augmented GnRH secretion followed by raised levels of serum LH and testosterone[38,39].

In a study by Csaba *et al*[40], administration of a single dose of endorphin to neonatal rats showed that sexual activity permanently decreased in females after five months and their tendency to refuse the male increased, in addition to male aggression increasing. Female rats showed a permanent increase in the density of uterine estrogen receptors, and male rats showed a decline in the serotonin level in the brain. Although little is known about the interaction of endorphin and other hormones or neurotransmitters in relation to human sexuality, results of the study by Csaba *et al*[40] suggest that there is a role for hormone imprinting at birth and that endorphin treatment influences sexual hormone production, which can affect sexual behaviors in later life.

During labor, the level of endorphin in the mother's blood increases and is dependent on the intensity of pain and the duration of labor[41]. Therefore, it is presumed that neonatal endorphin imprinting affects later-life events such as sexual activity and aggression, because of the association between brain serotonin levels and aggressive behaviours[42]. However, this hypothesis is based solely on data from rodent models, and its generalizability to other species, including primates (*e.g.*, humans) is currently unclear.

The opioid peptides impose their excitatory effects by acting in the ventral tegmental area, increasing the activity of the mesolimbic dopaminergic system and promoting sexual arousal and motivation. There appears to be no research investigating the role of beta-endorphin in human sexuality, making it impossible to determine whether this is a general effect of all opioid peptides or if it is specific for other peptides such as enkephalin, as reported in the literature[33].

Research in animal models has found that beta-

endorphin affects brain activity and maintains a sense of balance and wellbeing by allowing the animals to perform feeding and drinking activities as well as social grooming[43]. A systematic review of animal studies[44] has also suggested that beta-endorphin plays its main role in the appetitive and precopulatory phase of sexual behavior, in preparation for copulatory activities. Further, there is a relationship between beta-endorphin and sex hormones.

EFFECT OF OXYTOCIN ON SEXUALITY AND ROMANTIC RELATIONSHIPS

Human studies

Oxytocin is known as the "hormone of love". Endogenous oxytocin arouses feelings of pleasure, peace and security when in the company of a partner[45]. The release of endogenous oxytocin from the pituitary gland into the bloodstream is triggered by sexual stimuli such as hugging, touching, and genital and nipple stimulation in both genders, and its plasma level is correlated with the levels of arousal and lubrication, reaching a peak during orgasm[46]. The release of endogenous oxytocin decreases fearfulness and works as an anxiolytic agent, diminishing the level of anxiety through inhibiting fear responses in the amygdala, which contains substantial numbers of oxytocin receptors[47]. The release of endogenous oxytocin from the brain during intimate touching or sexual activity with a partner has been suggested to have a vital role in sexual monogamy in men and women[48].

Ecstasy [(3,4-methylenedioxymethamphetamine (MDMA)] is a recreational psychoactive drug and is often called the "love pill". Research has shown that ecstasy stimulates endogenous oxytocin activity *via* activation of serotonin 5-HT1A receptors resulting in an increase in feelings of love, empathy and connection to others[49].

A rise in endogenous oxytocin results in an increase of plasma endorphins, natural pain-killers that can diminish pain in women who suffer dyspareunia, due to anxiety or a lack of trust in their partner during the first stages of their relationship[50]. Despite these, research has suggested that endogenous oxytocin may not be high before the commencement of sexual activity and it may not be the main trigger of sexual drive and desire preceding the initiation of sexual activity. According to this, the level of endogenous oxytocin increases after the woman receives appropriate stimulation and starts enjoying the sexual activity[51]. This claim is supported by data from self-report studies indicating that some women may enjoy sexual activity and reach orgasm when sexual stimulation and intercourse occur[52], although they may not be the initiator of the sexual activity[53,54].

Higher plasma concentrations of oxytocin have been shown in people who have fallen in love as well as during the transition to parenthood. A magnetic resonance imaging study of 10 women and 7 men (mean age 21.4 years) has shown that brain areas involved in the formation of romantic attachment are rich in oxytocin receptors[55]. The same brain regions are activated in new parents with great parental-infant attachment and new lovers in prolonged romantic relationships[56]. These reports suggest that parent-child attachments and romantic bonds may share some fundamental mechanisms mediated by the oxytocinergic system, though it is not evident in the literature.

Postpartum loss of sexual desire, arousal and orgasm have been reported across many studies and have been shown to remain as long as one year[53] to many years after childbirth[57]. Research suggests that changes in sexual function in postpartum women may not be only because of physical changes during the transition to motherhood, but may also be due to psychological and neuroendocrine alterations during and after childbirth. Neuroimaging assessments of seven mothers have shown changes in the prefrontal-limbic system during the transition to motherhood, including the amygdala, which is responsible for the expression of oxytocin receptors, suggesting that the amygdala may be less responsive to sexual images and stimuli in postpartum women[58]. Another suggested alteration is that the brain may not release the expected amounts of endogenous oxytocin during sexual activity in postpartum women, and this may result in decreased self-reported feelings of sexual desire in these women[59].

A modest body of evidence suggests that any factor that can interfere with the release of endogenous oxytocin can cause sexual dysfunction in postpartum women. Among the various factors contributing to sexual problems in postpartum women[60-62] is the use of intravenous synthetic oxytocin during labour and birth. This factor is not subject to the standard mechanisms regulating endogenous oxytocin and affects the normal behaviors of the amygdala[63,64].

Considering the low levels of endogenous oxytocin in women experiencing sexual problems, and the different mechanisms of action of intranasal and intravenous synthetic oxytocin, researchers have attempted to address the sexual problems of women by using an intranasal spray of synthetic oxytocin which was supposed to deliver lower doses of synthetic oxytocin to the body compared with intravenous synthetic oxytocin administered during labour. A case report by Anderson-Hunt and Dennerstein[65] showed copious vaginal transudate and a subsequent intense sexual desire two hours after the use of intranasal spray of synthetic oxytocin to facilitate breastfeeding. However, findings of their report may not be generalised to the entire population as they studied only one woman for a short period of time. Another study showed that intranasal administration of synthetic oxytocin improved attachment-related behaviors, such as eye gazing[66], interpersonal trust, compassion and positive communication[67].

The use of intranasal synthetic oxytocin in men has been shown to result in a remarkable increase in their

endogenous oxytocin levels together with increased secretion of catecholamines when they were engaged in sexual activity in a laboratory setting[68]. Nevertheless, no further evidence in the literature supports the use of synthetic oxytocin for female sexual dysfunction.

As mentioned earlier, there are mixed reports regarding the impact of oxytocin on romantic relationships. Some studies have indicated links between plasma oxytocin and positive communication, affiliation, emotional support and love[69,70], but others have shown associations between elevated peripheral oxytocin and post-conflict anxiety and decreased levels of forgiveness in romantic couples[45,71]. These results, however, should be interpreted with caution due to controversy about the reliability of plasma oxytocin levels as a peripheral proxy for central concentrations.

Animal studies

A comprehensive review of animal studies on the effect of neuropeptides on the regulation of the brain, social cognitive processing and associated social behaviors has suggested a link between the oxytocinergic system and dopamine which promotes sexual behaviors such as pair bonding and sexual arousal[72]. This association may also contribute to an expectancy of future reward and the sexual arousal reward that are naturally expected later, as shown in rodents[73].

When synthetic oxytocin is administered intranasally, it proceeds through the fluid-filled perineural channels created by the cells ensheathing the olfactory receptor neurons. It then travels through the cribriform plate in the skull and reaches the CNS[74]. In their study on primates, Chang *et al*[75] showed increased levels of endogenous oxytocin in cerebrospinal fluid (CSF) after synthetic oxytocin spray inhalation, supporting the likelihood of central effects of synthetic oxytocin.

Unlike intranasal oxytocin, when intravenous synthetic oxytocin is administered, the blood–brain barrier inhibits it from reaching the brain and it therefore does not function as the "hormone of love"[74]. Other animal studies have reported that synthetic oxytocin may reach the brain, but it may act differently from the endogenous oxytocin and have different effects on the body[76,77]. They have shown that there is not always a correlation between peripheral and cerebral levels of oxytocin, suggesting that the two systems may be controlled independently and that intravenous synthetic oxytocin does not essentially raise oxytocin levels within the brain. Research on male prairie voles has shown inhibitory effects of synthetic oxytocin on pulsatile secretion of endogenous oxytocin that may last year[78].

CONCLUSION

There is a lack of up-to-date data on the mechanism of action of endorphins and their role in regulating human sexuality. Some animal studies report the effect of beta-endorphin on GnRH, LH and testosterone, but these findings have not been supported by human research.

A thorough review of the literature has identified inconclusive reports and many gaps in knowledge of the association between endogenous oxytocin and sexuality. Further to this, there is no strong evidence supporting the positive effects of synthetic oxytocin on human sexual function and relationships. Although research in humans suggests a central role of these hormones in sexuality, the most reliable findings to date involve peripheral activation, mainly based on animal research.

The importance of physiological changes during sexual activity and how they can affect human relationships, and the gaps in the literature on the topic, highlight the need for high-quality research to extend our understanding of the hormonal physiology of sexual function and the role of endorphins and oxytocin in human sexuality. To fill the gap, further future studies are required to investigate the role of these hormones in human sexuality and their mechanism of action in men and women.

The inter-relationship between these two endogenous hormones and human sexuality is still unclear and no previous research has explored this association. Further future research is required to apply a methodological triangulation of qualitative and quantitative methods for analysing determinants of various aspects of human sexuality considering the role of endorphins and endogenous oxytocin. While the qualitative analysis may focus on behavioural sex differences, the quantitative analysis concentrates on how the two endogenous hormones influence human sexuality and sexual behaviours.

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