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Title: The Role of Oxytocin: From Conception to Birth

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Abstract

Oxytocin is typically linked to birth and lactation, but there is increasing evidence about its role in the events leading up to conception and birth. Such events include its involvement in sexual behaviour and its effects on the menstrual cycle, both of which are important in human reproduction. New evidence in its involvement in birth and lactation will also be included. Essentially, this review aims to link all these events that oxytocin is involved in from conception to birth.

Keywords: oxytocin, oxytocin receptor, behaviour, reproduction, birth, lactation

Introduction

The nine amino acid hormone called oxytocin, its origin coming from the words meaning "quick birth", has long been known for its role in contracting the uterus. However its properties go into effect long before birth and last till long after. [1]

Oxytocin, according to studies up till now, has a single receptor. [2] The most popular antagonist of this receptor, Atosiban, is mainly used clinically to manage premature labour. Its induction of activity in the very similar vasopressin receptor however, has resulted in focus on the production of antagonists, as well as agonists, which are specific only to oxytocin's lone receptor. [3] In fact, newer antagonists made from non-peptide substances, may soon be used in practice due to their increased specificity to oxytocin's receptor. [4] Picotin, a peptide agonist, is administered for induction of delivery, and to aid lactation. [5] As with antagonists, non-amino acid agonists, are being created. [3]

There is also a difference between sexes in the production of oxytocin as well as its receptors within the body. The expression of either has been found to be much more pronounced in females, in itself implying that its properties could be determined by steroid hormones. [6] In an experiment involving rats, it was only the female offspring which had more pronounced levels of receptor production in response to stimulation from the mother. [7] With regard to distribution in the brain, areas where oxytocin is involved with behaviour, like the ventromedial hypothalamic nucleus, show a difference in the level of binding of oxytocin, while some areas like the amygdala's central nucleus, shown none. [8]

Sexual Behaviour

Oxytocin (OXT), released as a result of genital and breast stimulation, and its function have been implicated in sexual behaviour or activity, a process basic to reproduction. [9; 10] During sexual arousal, OXT levels in the blood increase in both males and females, and levels have been noted to increase even further in ejaculation and orgasm. [11] The correlation between electromyography

intensity and OXT has been shown to be highly positive, in males and females, before and during orgasm, a mechanism regulated by intranuclear OXT in the paraventricular nucleus (PVN). [12]

The OXT-dopamine (DOPA) neural pathways in the brain, are also involved in the motivation and reward system in the phase of anticipation of sexual activity, and not just erectile function and intercourse. [13] The interaction of OXT with the DOPA and serotonin systems, is what determines whether sex is successful. Lack of orgasm, sexual impotence and loss of sexual drive, can occur if there are defects in the interaction of OXT with these systems or in the OXT secreting system itself. However, if these systems are activated too much, multiple orgasms or abnormal desires may result. [10] In fact, due to the function of OXT in postpartum women which makes them less reactive to stimuli, these women are less interested in sex. [10]

Thus, OXT levels in the blood and its many functions, are important in the maintenance of sexual behaviour. [10]

Female Sexual Behaviour

A rise in OXT levels was observed in many female mammals, including rats, sheep, rabbits and even humans, after vaginocervical dilation. Particularly in rats and sheep, after oestrogen administration, vaginocervical stimulation resulted in increased OXT levels centrally. [14]

Gonadal steroids in female rats, control the two versions of sexual behaviour, be it solicitous, or receptive by lordosis. [15] When female rats, which are primed with oestrogen, are then infused with OXT intracerebrally in the hypothalamus, these two processes are both facilitated. [16] Some studies suggested an infusion of progesterone was required in order for the infusion of OXT to aid lordosis. [17] However, female rats being primed for three days with oestradiol lead to lordosis even without progesterone administration. [17] After it was noted that the sites of where OXT is administered affect duration and/or frequency of lordosis, it was suggested that OXT dictates traits of lordosis. [18] Also, when low levels of OXT is introduced into the lateral ventricle, lordosis was subdued. [19] It has been established that endogenous OXT is necessary for sexual behaviour, through studies with administration of OXT antagonists before progesterone. It was observed that when OXT antagonists were administered, female rats were less sexually receptive and therefore there was increased rejection. [20] When OXT is infused in female rats with intact ovaries in natural

estrus, lordosis duration and frequency is heightened, while OXT antagonists suppress this effect. It was noted that when female rats are primed with oestradiol only, OXT antagonists have no effect, suggesting that OXT antagonists reduced only the effects of sexual behaviour which are brought about by progesterone. [21]

Noradrenaline release into the ventromedial hypothalamus induced by OXT, was enhanced by steroidal priming. This most likely happens by a peripheral mechanism which drives lordosis by further exciting ventromedial hypothalamus neurones. [22]

Only a small number of studies have been conducted on other species apart from rats. In oophorecomised hamsters , priming with oestradiol and injecting their hypothalamus with OXT makes them more receptive sexually, while injecting them with OXT antagonists results in suppressed sexual receptivity. [23] In addition, OXT infusion into the hypothalamus results in heightened ultrasonic vibrations which are used by the female hamsters to signal and entice possible mates. [23] In prairie voles, females which have not been exposed to males after weaning, and had OXT administered everyday for five days, were more likely to mate than alike females which had saline injected instead of OXT. OXT co-administered with oestrogen made females more receptive than with oestrogen injections alone. [1] However, in female mice which are OXT deficit, there seemed to be no impediment to normal sexual behaviour, and the resultant pregnancy and parturition, with pups dying only after difficulties in lactation. OXT did have an ameliorating effect on labour being unsettled by circadian rhythms, being reset. [24]

Male Sexual Behaviour

Most studies on male sexual behaviour have been carried out on rats and are based on many aspects, including penile erection, ejaculations, duration and/or frequency of mounts and even yawning. Yawning has been found to be a stereotypical act which either happens alone or linked with penile erection. [25] OXT was noted to be involved in inducing penile erection in many mammals, including monkeys and rats. [26] Injection of low levels of OXT into the PVN is capable of inducing penile erection and yawning in rats. [27] These actions can be suppressed by administration of OXT antagonists and by electric lesion on the PVN. In rodents without oxytocin receptors there was a less likelihood of ejaculation, as well as a higher level of stimulation needed to reach sexual arousal in comparison with the control. [28] Some clinical trials have used this theory in order to

investigate the possible use of oxytocin antagonists in premature ejaculation. [28] However, there are studies which show that treatment with an oxytocin antagonist has results that are not significantly different from treatment with a placebo, despite the drug being safe. [29]

Although rare, the reverse of premature ejaculation, that is, delayed ejaculation, can be of great concern to those who suffer from it. Treatment with oxytocin, based on the reasoning above, has been investigated in many trials. [30] In one such study, treatment with oxytocin intranasally before manual stimulation showed that while the drug was well tolerated and the length of time needed to ejaculation was reduced, there was no significant difference when compared to the placebo group. [31] It has been shown that yawning can be suppressed by opioid peptides, as it is induced by OXT released by OXTergic neurones activated by DOPA agonists or OXT, which are at a distance from the PVN. [25]

There was a noteworthy effect on the waiting time required to reach ejaculation, in that it was reduced, as was the interval of postejaculation, by the introduction of central OXT. The reduction in testosterone in male rats which were significantly older, may explain why the effect of injected OXT seemed stronger. [32] However, if castration has occurred in male rats, and therefore there is an absence of testosterone, then OXT has no effect on inducing penile erection, and only on administration of testosterone along with OXT does erection occur. [24]

Levels of OXT which are too high or too low seem to inhibit the frequency of erection, while moderation of the OXT levels seemed to be optimum for sexual activity. [24] One reason for high levels of OXT being an inhibition to erection, may be that OXT induces sexual satiety at such high levels. OXT released while mating in the PVN, may contribute to this sexual satiety by inducing a sense of non-anxious behaviour up to half an hour after copulation. [1]

A hypothesis of nitric oxide (NO) synthase activity being increased in oxytoginergic neurone cell bodies by OXT in order to elicit sexual activity, was postulated. [25] NO synthase is stimulated by intracellular Ca^{2+}, and therefore Ca^{2+} voltage-dependent channel blockers introduced into the PVN can suppress penile erection and yawning induced by OXT. [15] When OXT antagonists were

injected, penile erections elicited by NO donors in the PVN, were subdued. [33] In summary, penile erection can be elicited by NO synthase activation by OXT in the PVN, and the resultant NO produced may stimulate the oxytocinergic neurones which project into areas such as the spinal cord, controlling male sexual behaviour. [15]

The bulbocavernosus muscle is innervated by a sexually dimorphic motor nucleus in the spinal cord which communicates with the OXTergic neurones in the PVN. This muscle is involved in penile reflexes, so it might be that this particular pathway is used during copulatory mechanisms which are instigated by the hypothalamus. [34]

As with some female studies, not all experiments confirm that OXT aids male sexual behaviour though. Some studies show that all male sexual activity was suddenly stopped on administration of OXT in prairie voles, and such effects lasted a whole day. [35] The postejaculation interval time was lengthened on central injection of OXT. All these point to the theory that OXT may also promote animals in becoming sated sexually. [15] Also, in OXT knock out male rats, litter size is normal, indicating that there are other mechanisms and hormones involved in sexual behaviour, which still allow the male rats to interact sexually with females. [24]

Sexual Behaviour in Humans

Central OXT levels are raised during sexual stimulation and arousal and reach the maximum level at orgasm in humans. [11] However, it has been noted that plasma levels of OXT in males are not particularly raised during sexual arousal, but they are markedly increased during ejaculation, reaching a peak before falling back to their original levels after half an hour. [36] Self stimulation by men after administration of an opioid antagonist resulted in lower levels of OXT and the level of arousal and subsequent orgasm. [15] In human females, similar measurements were encountered during and after orgasm, where OXT levels reached their peak. [37]

A woman, taking daily oral doses of a contraceptive pill which contained oestrogen and progesterone, participated in a study using intranasal OXT, which seemed to enhance the intensity of arousal and orgasm after stimulation of sexual organs. [38] OXT might also be involved in the stimulation of contraction of smooth muscle in the area of the pelvis. This was suggested after

there seemed to be a high correlation between OXT plasma levels and muscle contractions which occurred during orgasm. [12]

Apart from the effect on reproductive organs, OXT might also have an effect on neurones involved in the cognition of feelings involved in orgasm, and could ultimately effect sexual performance in humans. [15]

FEMALE REPRODUCTIVE PHYSIOLOGY

Uterus

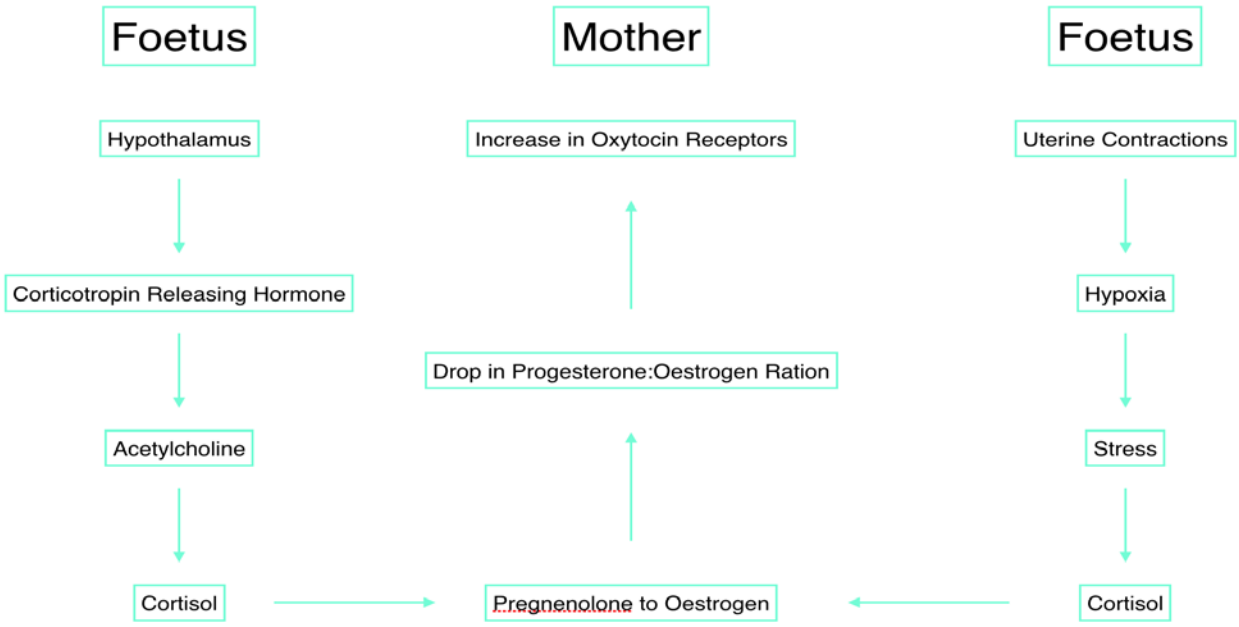
The uterus is a classic target for OXT, which is the most effective uterotonic agent, and a reason why it is used during labour clinically. Alternatively OXT antagonist can be used to delay premature labour and as a treatment for dysmenorrhea. [3] In studies on rats, the OXT gene was found to be expressed at term in uterine epithelium. [15] This increase in OXT messenger ribonucleic acid (mRNA) caused by oestrogen, was only for three days and reached concentrations far higher than OXT released from the hypothalamus. [39] The OXT gene seemed to be expressed in the cells of the amnion and placenta in rats, while in humans it was noted to be expressed in the amnion, decidua and chorion. [40] Most studies though, found that there was no OXT increase of note in intrauterine tissues or maternal blood before the start of labour. Despite this, some studies suggested that there is a correlation between the progression of pregnancy and the OXT secretion pattern. [15] A study on rhesus monkeys found a positive correlation on the concentrations of maternal OXT and nocturnal uterine activity, which increased further along the pregnancy and during labour. [41]

The sensitivity of the uterus to OXT increase significantly during the start of labour. [15] This occurs by a larger density of OXTRs in the myometrium and an upregulation of the OXTR mRNA, both of which reach their highest levels at the onset of labour. [42] These levels increase by a factor 200 from the norm in both female rats and humans which are not pregnant. This results in OXT's effects on the uterus to cause contractions during labour, to be even more potent, and thus stronger contractions are produced, than in a non-pregnant female. Following the delivery of the offspring, the levels of receptors decrease back to normal levels and density in a rapid state. [43] This might be to prevent unnecessary contractions during OXT release for the initiation of lactation. [15]

As can be seen by the progesterone to oestrogen ratio in plasma decreasing during the days before the onset of labour, gonadal steroids seem to have an influence on OXTR regulation in uterine tissues. However, in humans a drop in progesterone is not seen till after the delivery of the placenta, therefore there seems to be an increase in oestrogen, in order to achieve a drop in the gonadal steroid ratio. [15] This has been found to be achieved in many ways, for example in sheep and bovine, as the hypothalamus of the foetus matures, an increase of corticotropin releasing hormone results, leading to a release of acetylcholine. [42] This secretion of acetylcholine stimulates the release of cortisol. Furthermore, uterine contractions induced by OXT, may decrease blood flow temporarily and cause foetal hypoxia, inducing a stress release of cortisol. [15] The cortisol released induces the action of a cytochrome enzyme which activates placental turnover of pregnenolone to oestrogen. [15] Additionally, in primates, corticotropin releasing hormone secreted by the placenta induces foetal release of dehydroepiandrosterone sulfate, which can be converted to oestrogen. [44] This is illustrated in figure 1.

As a result of the decrease in progesterone levels, the inactivation of the uterus which it was maintaining ceases, allowing parturition to commence. [15] Figure 1. The two processes which may

The two processes which may induce an increase in oxytocin receptors



induce an increase in oxytocin receptors.

Apart from the increase in OXTRs in the uterine tissues, there is also an increase in gap junctions, leading up to birth in humans. [45] Of course, the responsiveness to OXT is different in different patients, and sometimes in those same patients from one day to the next. [15] For example, some patients only require a small dose of OXT to induce a hypertonic uterus, while others are completely unresponsive to even high doses of OXT, administered in order to induce labour. [46]

Several studies suggest that progesterone inhibits OXT effect, and induces relaxation of the uterus. [15] Progesterone induces a decrease in OXT binding in the uterus, and a decrease in of OXTRs by downregulation. The OXTR increase is not only found in the uterus, but also in the decidua, in fact, during labour the expression of OXTR genes increases by a factor of five in the human chorionic decidua. [47] In the decidua, OXT promotes the secretion of prostaglandin F2alpha. [15] Close to labour in rats, progesterone levels drop in order to initiate parturition, this is achieved by an increase in concentration of prostaglandin F2alpha, which activates luteolysis, which leads to progesterone levels declining. Mice without the prostaglandin F2alpha receptor gene could not deliver normally despite a normal development. These mice showed no response to OXT and their OXTRs were not stimulated. [48] As a result, there was no withdrawal of progesterone. [15] Removal of ovaries in these prostaglandin F2alpha receptor deficient mice, made a normal delivery possible due to a resulting normal stimulation of OXTRs. [48] This implies that stimulation of OXTRs, is the key to onset of labour, and that the OXT system regulates labour. [15] Despite this, other studies have noted that labour proceeds as normal in OXT knock out mice, suggesting that OXT isn't the only substance that initiates contractions in the uterus. [49]

Mice having an absence of the gene for cyclooxygenase 1, an enzyme which participates in the production of prostaglandins, typically have low levels of prostaglandin F2alpha. This delays onset of parturition, due to no significant fall in progesterone because of difficulties in luteolysis. [50] However, mice which have both an absence of the gene for cyclooxygenase 1 and an absence of OXT, proceed into labour normally. This could be because of the counter effect of the functions of prostaglandin F2alpha and OXT, with the former being involved in luteolysis, and the latter being luteotrophic. [50] Therefore, OXT maintains the production of progesterone before parturition, while prostaglandin F2alpha negates the luteotrophic effect of OXT when the normal onset of labour

must be initiated. [50] This explains why there is a rise in OXTRs in the uterus rather than an increase in OXT, as the latter may prolong pregnancy due to its luteotrophic effect. The former however, would still allow for the uterotonic effect by OXT. [15]

Studies on bovine animals found that the endometrium had higher levels of OXTRs mRNA than the myometrium during the equivalent part of the cycle. At oestrus, these levels are found to be equivalent to the levels noted during the end of pregnancy, but for the rest of the cycle, levels of OXTRs are not detected. [51] OXT promotes the secretion of prostaglandin F2alpha in ruminant animals in late diestrus, which leads to degradation of the corpus luteum, starting a new oestrus cycle. Therefore, the uterus, with OXTRs, can control the duration of the luteal phase. The cycle can be lengthened by delaying the initiation of luteolysis with OXT antagonists or continuous OXT, which causes a downregulation of OXTRs. [52] In ruminants, before the start of labour, there appears to be a significant increase in OXTRs in the endometrium. Interferon-gamma, secreted by trophoblasts, and other anti-luteolytic peptides, inhibit the expression of endometrial OXTR gene in the endometrium. [53] In primates however, the uterus does not seem to be required for luteolysis, as even after removal of the uterus, the ovaries still function as normal. [15] In humans, OXTRs mRNA was found in the endometrium, the ovary, and the myometrium of pregnant females, while in non-pregnant females it was found in the endometrium, where they reached a peak during ovulation. [54]

Multiple studies have suggested that there is a paracrine system in human intrauterine tissue which produces and secretes OXT. [55] The maternal decidua, chorion and amnion, all of which are constantly in contact with amniotic fluid, are able to transfer to the myometrium, signs of foetal and maternal origin. The chorion and amnion have the ability to synthesis steroids, and so play a role in the progesterone to oestrogen ratio. [56] In pregnant bovines, OXT mRNA levels were insignificant in areas other than the corpus luteum, and after the start of labour, OXT levels were extremely significant in the corpus luteum. OXT which originated in the pituitary, may be complemented by the luteal OXT. [51] Therefore, during labour, OXT may mainly act locally not centrally. [15] The paracrine system of the uterus can therefore secrete OXT, sex steroids and prostaglandins, without having levels mirrored in maternal blood. [55]

Ovary and Corpus Luteum

The ovary in multiple species may produce OXT as the hormone has been found inside the organ. [57] In a particular species of monkey, some studies imply that OXT participates in luteinizing follicles. Most granulosa cell layers in antral follicles contained OXTRs and OXT itself, after treatment with human chorionic gonadotropin (HCG). [15] Only granulosa cells which came from pre-ovulatory follicles synthesised OXT, and only these cells had a rise in progesterone synthesis. [58] It was found that OXT is involved in the development of the blastocyst in mice and so is involved in the early phases of development of the embryo. In humans, OXT and its receptors are found in cumulus cells which surround the oocytes. Therefore this local OXT may also take part in human embryo development. [59]

Endometrial OXT and neurohypophysial OXT interact in order to promote the release of uterine prostaglandin F2alpha, which occurs in pulses. It was theorised that central OXT pulses regulate luteolysis. The uterus therefore converts signals from transient hypothalamic OXT release to luteolytic prostaglandin F2alpha in pulses. Luteal OXT is secreted at the same time by prostaglandin F2alpha in ruminants, producing a loop of positive feedback which augments the signals from OXT. [60] OXTRs in the endometrium controls this feedback loop. In order to avoid corpus luteum degradation and progesterone drop in pregnancy, endometrial secretion of prostaglandin F2alpha into maternal blood must be impeded, this is done by the growing conceptus. This is necessary as progesterone is important for establishing and maintaining pregnancy. [15] Luteal cells can be activated by OXT, but they can also synthesis it. [61] OXT secretion seemed to have the highest levels in the early corpus luteum, in most species, implying that OXT mainly acts on this early phase of the corpus luteum. [62] OXT's effect on the corpus luteum were also dependent on its age. [15]

All through the menstrual cycle, in a typical, healthy woman who is still fertile, OXT in plasma fluctuates, with the highest levels being during the ovulatory and follicular phases, and being lower in the luteal phase. [10] The luteinizing hormone surge is promoted by OXT, therefore, OXT antagonists can inhibit the surge from reaching its full potential. This means that there is involvement by the significant level of OXT just prior to the luteal phase, in the regulation of luteinizing hormone, meaning OXT is involved in balancing ovulation and a resultant pregnancy. [10]

Neurochemical Mediators

While it seems that there is no rise in the basal level of intranuclear OXT secretion during pregnancy, it has been found that the sensitivity of central OXT is augmented, and that opioids and noradrenaline control intranuclear OXT together during gestation. [63]

Noradrenaline

During gestation, there is a rise in both central OXT and noradrenaline secretion in reaction to noradrenergic activation. [63] New studies showed that in the dorsal SON, there is noradrenaline secretion after activation of intraventricular cholecystokinin axons of magnocellular neurones, which is much higher in pregnant females on days twenty one and twenty two of gestation, in comparison with day twenty of gestation, and non-pregnant females. [64] Additionally, reactions of intranuclear OXT to excitatory stimulation of noradrenergic receptor induction are augmented during pregnancy. [63] It was noted that with introduction of an alpha1-adrenergic agonist, there was a larger release of OXT both systemically and intranuclearly, during the last stages of pregnancy than in the intermediate stages or in non-pregnant female rats who have had their ovaries removed. [65] This shows that even though base levels of systemic OXT remain unchanged during pregnancy, both intranuclear OXT reaction and central noradrenaline reaction to adrenergic activation in magnocellular nuclei have an increased effect. [63]

Opioids

Studies show that systemic OXT release is inhibited by opioids during the end of pregnancy. [66] When an opioid antagonist was introduced in this same stage of gestation, SON OXT levels seemed to rise, implying that opioids also effect intranuclear OXT release. [67] But during labour, this opioid antagonist had no effect on OXT levels intranuclearly. [68] These studies show that opioids cause inhibition of OXT release on the days prior to labour but not on the actual day. [66]

The above explains how noradrenaline and opioids work together, in the late stages of pregnancy, opioids inhibit central OXT release to impede systemic OXT release by noradrenergic activation

from happening too soon. The withdrawal of the opioids effect of inhibition when labour happens, could then let the systemic and central OXT secretion by noradrenergic activation occur. [63]

Of course, the excitation and inhibition of the OXT system may not be the same all through pregnancy. Probably the excitation process occurs during the early stages of pregnancy until the intermediate stages in order to accustom the system to the needs of labour and lactation. [63] When labour nears, opioids start to inhibit OXT release in order to impede premature labour. [63]

Preterm Labour

Preterm is a common complication encountered by obstetrics and oxytocin antagonists have long been in use. One such antagonist is atosiban, whose mode of action is inhibiting the increase of calcium intracellularly, leading to decreased contraction of uterine muscle. [69] Atosiban seems to be very well tolerated with a very low risk of side effects. Of these side-effects only the mother's effects have been noted, and the side effects mentioned are very mild. No effect on offspring was noted, even after a follow up of two years. [70]

Postpartum Haemorrhage

Postpartum haemorrhage is the cause of one quarter of maternal deaths during parturition. Management by administration of OXTR agonist, Pitocin, is one possible treatment for postpartum haemorrhage. [71]

Pitocin is administered after delivery of the baby, in order to stimulate contractions of the uterine muscle, aiding the delivery of the placenta, and therefore reducing the volume of blood lost until its expulsion from the body. [71] Since atony of the uterus is the most frequent cause of postpartum haemorrhage, administration of a uterotonic agent such as pitocin, is an efficient treatment option. [72]

Recent studies have shown that an addition of misoprostol to the oxytocin dose seems to be beneficial in controlling haemorrhage, due to it being a prostaglandin E1 analogue, and therefore uterotonic as well. [73] However, the use of misoprostol alone seemed to be no different from the use of placebo, indicating that oxytocin is still superior with regard to uterotonic activity. With

regard to caesarean section, a continuous infusion of oxytocin after a bolus injection seemed to require less use of uterotonic medication when compared to a bolus injection without infusion. [74]

In post-abortion care, there is evidence that adding oxytocin to the dose of mifoprostol, reduces the mean expulsion time in uterine evacuation. [75] This in turn reduces the risk of haemorrhage.

Lactation

Lactation, or milk secretion by mammary glands due to the suckling of young, is an essential mechanism for infant mammals to survive. [10] Lactation is brought about by the milk-ejection reflex, a process dependent on hypothalamic OXT. [76] The importance of the milk-ejection reflex is shown through an experiment with OXT-deficient/knockout mice. These mice cannot achieve the milk-ejection reflex, and therefore cannot suckle their young, so while parturition proceeds as normal, lactation presented with defects, leading to high pup mortality rates. [77]

Apart from simply providing nourishment to the infant, breastfeeding can also reduce the risk of infant development of many diseases, such as infections, obesity, sudden infant death syndrome and type 2 diabetes, among others. The mother also benefits, with reduced risk of breast and ovarian cancers, and type 2 diabetes. [78]

Milk Ejection Reflex

When an infant stimulates the nerve endings of the nipple through suckling, the sensory impulses created travel through the spinal cord to the synchronisation centre in the hypothalamus. [79] The supraoptic nucleus (SON) and the PVN have OXT neurons, which are activated by this centre at the same time. These release OXT which lead to milk ejection from mammary glands. [80]

OXT is released in high frequency bursts which are synchronised, each action potential lasts about four seconds, with an interval of five to fifteen minutes between bursts. [15] After OXT is released into the bloodstream and it reaches the breasts, it stimulates lactiferous ducts, breast tissue alveoli, and sinuses, most particularly the myoepithelial cells in their walls, causing contraction and the ejection of milk. This all occurs within a minute from the start of suckling. [15]

The high frequency bursts which occur in a pulsatile pattern, ensure an efficient mechanism of milk ejection reflex, due to the avoidance of desensitisation of the OXTRs. The pulses ensure that there is minimal fatigue from release of OXT while at the same time, facilitate OXT release. [81]

In human females this reflex can also be initiated without contact, for example by the sound of an infant crying. [82] Also along with continued milk removal, OXT is necessary for the proliferation of breast tissue alveoli and the functioning of the mammary glands. This fact was shown through an experiment with OXT-deficient dams, as while at parturition, alveolar density of both the wild types and the OXT deficient dams were the same, half a day after parturition, there was proliferation of alveolar cells in wild types, but no proliferation in OXT-deficient dams. The lobular-alveolar units expanded when there was continual removal of milk in wild types, but there was no such effect in OXT-deficient dams. [83] Furthermore involution of mammary tissue was noted in OXT-deficient dams even though continuous milk removal still occurred. [83]

Plasticity in the Supraoptic and Paraventricular Nuclei

The SON and PVN undergo changes in morphology during pregnancy and lactation, such as astrocyte processes being withdrawn from the nuclei, synaptic contact becoming increased, as well as the increase of direct membrane apposition of neurons. [81] Dye-coupling studies have revealed that gap junctions are present in magnocellular neurons. The incidence of dye-coupling also seems to increase during lactation, suggesting that the presence of these gap junctions may aid in the synchronicity of OXT pulsation. [84] The three transmitters: GABA, glutamate, and noradrenaline, are used in the OXT system during lactations. [81]

Oestrogen and progesterone seem to control such plasticity during the last few weeks of pregnancy. These increase until a couple days before birth, when progesterone levels drop and oestrogen levels are maintained till parturition. [85] While the plasticity involving the largest changes occur during parturition, most of the reorganisation is completed during late pregnancy. Early removal of young can reverse the changes in plasticity, which is maintained during lactation. [81] Since oestrogen and progesterone are enhanced by OXT, central OXT may act in a paracrine way,

therefore synaptogenisis may be promoted by OXT, most likely by the enhancement of excitation achieved by neurotransmitters. [86]

In the SON and PVN, an upregulation of OXT mRNA occurs in late pregnancy. OXT release in the SON and PVN does not increase in pregnancy however, despite the change in OXT mRNA during gestation, which may occur in preparation for parturition and lactation. [81] However, there is evidence showing that OXTR binding in the SON is increased. Since sensitivity of the system is increased by upregulation of OXTRs, any blocks in central OXT release during gestation can be better compensated for by OXT released by suckling reflex. [87]

Neurochemical Mediators

When an infant suckles, a number of neurotransmitters, namely: Noradrenaline, histamine and excitatory amino acids, are involved in the peripheral release of OXT. [63]

Noradrenaline

It has been long known that for systemic OXT to be released during lactation, the CNS noradrenergic system must be activated, but its involvement in the maintenance of levels of OXT intranuclearly has only recently been studied. [88] Noradrenaline was found to increase in the PVN, by the use of microdialysis, when a suckling stimulus was applied, and this was linked to an increase of intranuclear OXT. [68] This demonstrated that noradrenaline is implicated in both peripheral release of OXT as well as central. [63]

In other studies, if alpha- or beta-adrenergic antagonists are administered using retrodialysis, there is no release of central OXT in PVN despite a suckling stimulus being applied. On the other hand, if alpha- or beta-adrenergic agonist is administered, OXT release is increased intranuclearly without a suckling stimulus. [89] This showed that activation of the CNS noradrenergic system is required for the release of central OXT during suckling, similar to how it is required for systemic OXT release. Also, this shows that it is the central OXT system which initiates systemic OXT release. [63]

Histamine

Peripheral release of OXT during lactation, not only requires the activation of the central noradrenergic system, but also the activation of central histaminergic system. Lactating rats were used to demonstrate that, like noradrenaline, histamine concentration in the PVN increase in response to a suckling stimulation, and histamine receptor activation is necessary for release of intranuclear OXT, and ultimately systemic release of OXT. [90] Studies involving the administration of H1 or H2 antagonists, prevented the release of OXT in the PVN when a suckling stimulation was applied. This proved that histamine receptor activation is necessary for the release of OXT in the magnocellular nuclei, and ultimately systemic OXT release. [63]

Furthermore, central noradrenergic activation during suckling, is achieved by CNS histamine release. [91] This was demonstrated by the administration of histamine in the PVN, which evoked the release of intranuclear and systemic release of OXT, but when a noradrenaline antagonist called phentolamine was administered by retro-dialysis, no OXT was released intranuclearly, and therefore neither systemically. [91] All this shows that during suckling, the CNS histamine release induced, leads to the secretion of noradrenaline, which is required for the release of central OXT, and finally the release of peripheral OXT. [63]

Excitatory Amino Acids

Some amino acids, such as glutamate, are necessary for systemic OXT release during suckling. [91] Through the activation of AMPA receptors, the glutamergic system is in some way involved in the noradrenergic one. Studies have shown that an alpha-1-adrenergic antagonist can be used to prevent systemic OXT release induced by AMPA agonists. [92] Other studies have shown that glutamate increases OXT release by dendrites, through the investigation on hypothalamic slices, from rats which were lactating, ex vivo. A pre-synaptic action, induced by all this, suppresses GABA activation, thereby enhancing the OXT system activity of neurosecretion. The glutamergic system, though, has no effect on the concentration of OXT inside PVN, as shown through the local introduction of glutamate in the magnocellular nuclei. [93] This therefore suggests that glutamate may induce pulsatile OXT release in some other way which cannot be detected by microdialysis,

unlike noradrenaline and histamine. It may be that glutamate stimulates systemic OXT release without involvement from intranuclear OXT. While it is clear that excitatory amino acids are necessary for systemic release of OXT during lactation, and that the activation of the noradrenergic system is involved to mediate it, how exactly they are involved in the release of OXT in the magnocellular nuclei has yet to be determined. [92]

Stress

The stress response system and its neurons are effected by rising levels of OXT in the brain. In fact, lactating females react less to stressors and are ultimately less anxious than females which are not lactating. Furthermore as a reaction to stress, OXT levels rise, a possible defense mechanism, to prevent stress from continuing. [94] This can be shown when synthetic OXT is administered, and decreasing levels of cortisol and adenocorticotropin releasing factors are noted after. On the other hand, when OXT antagonists are administered to rats, cortisol levels are noted to increase. This is relationship is less clear in humans, however. [94] Before eating, as a preparation of breastfeeding, OXT levels in lactating human females are noted to be high, and HPA hormone levels are noted to be decreased after, as soon as breastfeeding is started. [95] These changes are most likely due to the effect the rising OXT levels in the brain have on the neurons of the stress response system, and those of the HPA axis. When compared to women who aren't breastfeeding, lactating women have a reduced heart rate and blood pressure when responding to stress, suggesting the latter have an increased vagal tone. [96] The vagus nerve detects rising levels of OXT, and pass on the information to the brain through afferent pathways. [94]

Looking at stress from a different perspective, it can be the cause of impaired lactogenesis, and subsequent breastfeeding attempts. First and foremost, OXT release, essential for the milk-ejection reflex, can be impaired by maternal stress. [97] Down regulation of milk production, due to the incomplete removal of milk from the breast, would result. Alternatively, during a particularly stressful labour, or due to complications, infants may be too weak to suckle effectively, leading again to incomplete milk removal due to no induction of the milk-ejection reflex, despite there being no complications with the mother. [97]

The pathway could also be reversed, if onset of milk is delayed due to non-stress related complications of lactogenesis, the mother may become stressed, and in reality it is difficult to discern which of the factors came first, whether it was the lack of lactogenesis, or the stress. [97]

Synthetic OXT

It has been implicated that the use of synthetic OXT and epidurals during labour may negatively affect a mother's ability to successfully breastfeed, and as a result those mothers are more likely to start bottle feeding once at home. [94] One study suggested an inverse relationship between the dose of synthetic OXT used in order to induce labour or augment it, and the duration of breastfeeding exclusively. [98]

An explanation for why synthetic OXT may reduce the chances of successful breastfeeding could be, that while on a drip of synthetic OXT during labour, the nerve endings of the nipple may become desensitised, reducing the effect of the milk-ejection reflex. [99] Also such high synthetic OXT levels may affect the female's natural OXT system, giving feedback to the brain, which would result in less OXT being released during a suckling reflex, due to a weaker response. Furthermore, the high levels of synthetic hormone might enter the foetus, and subsequently the foetal brain due to an open ductus venosus and a weak blood-brain barrier, altering the infants behaviour because of a still developing brain, and maybe, the way it acts during suckling. [100]

However, due to the use of epidurals during most labours used in studies, it is difficult to discern how synthetic OXT exclusively effects breastfeeding.

Figure 2 provides a summary for all the factors which might effect lactogenesis.

Example of the inter-relationships among variables that may affect lactogenesis.

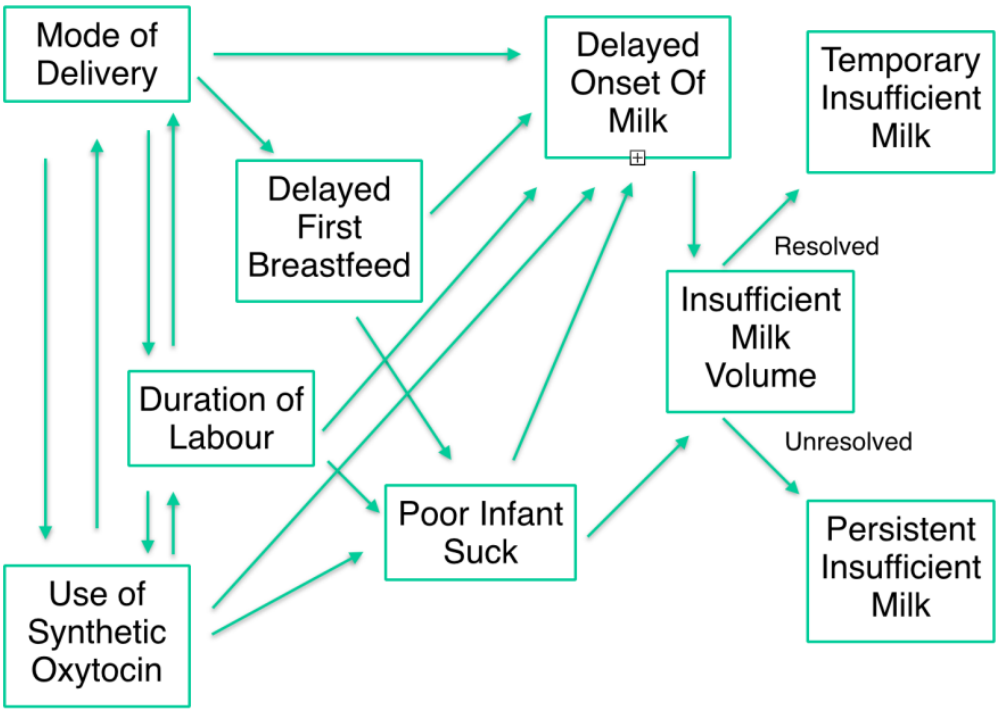


Figure 2. Adapted from a figure in 'Maternal and Fetal Stress Are Associated with Impaired Lactogenesis in Humans' (Dewey 2001)

Conclusion

In conclusion, oxytocin's many properties implies the great role it has in the propagation of life. And this review brings together the many roles oxytocin has with regard to bringing about life, from its start in the sexual behaviour which brings about conception, to the influence it has on the female reproductive organs leading up to birth and finally to its very prominent role in lactation.

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