Chapter

Oxytocin and Pregnancy

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Abstract

Oxytocin, an important neuropeptide, exerts a wide influence on the central nervous system and the peripheral tissues. In the central nervous system, the oxytocin gene expression is mainly shown to be present in neurons in the hypothalamic paraventricular and supraoptic nuclei. Oxytocin gene also transcribes in the peripheral tissues such as uterus, placenta, and amnion. Oxytocin receptors can be founded in many tissues in humans, like the uterine, ovary, testis, kidney, and so on. And just in the same tissue, due to the variation of physiology factors, the amount of oxytocin changes a lot. Oxytocin secretion is closely linked with pregnancy advancing. During labor, the contractions of uterine smooth muscles and oxytocin secretion are inseparable. Moreover, oxytocin is also responsible for stimulating milk ejection after parturition. Oxytocin is associated with many diseases. Poor regulation of oxytocin may cause postpartum depression and infantile autism. In terms of physiology, fatal heart failure and gestational hypertension are concerned with oxytocin level. In this chapter, we will discuss the oxytocin in pregnancy as well as its clinical applications.

Keywords: ovary, oxytocin, pregnancy, parturition, reproductive tissues, testis, uterine

1. Introduction

Oxytocin (OT) is crucial to pregnancy which exerts an important physiological influence on the central nervous system and the peripheral tissues [1]. Some findings suggest that OT secretion is closely linked with pregnancy advancing. And during labor, the contractions of uterine smooth muscles and OT, as well as its receptors, are inseparable. Moreover, OT is also responsible for stimulating milk ejection after parturition.

OT receptors founded in many tissues in humans, like the uterine, ovary, testis, kidney, and so on, are also important to pregnancy. Due to the variation of physiological factors during pregnancy, just in the same tissue, the amount of OT receptors differs a lot. Further studies illustrate that the oxytocin receptor (OTR) expression appears to be regulated at the transcriptional level [2].

And as such, OT disorder is associated with many diseases. To behavioral effects, poor regulation of OT may cause postpartum depression and autism spectrum disorders. In terms of physiology, premature delivery and dysmenorrhea are concerned with OT levels. Therefore, the clinical application of OT is also worthy of attention.

2. Oxytocin and its receptors in physiology

2.1 Male reproductive tissues

OT plays a physiological role in the male reproductive tract across species. In the human [3], OT messenger RNA (mRNA) and peptide itself are distributed in the testis where OTR has also been identified in the Leydig cells and Sertoli cells. But it is important to note that the species-specific differences in the case of the localization of the OT system in the male reproductive tract. For instance, in normal mice, testicular OT mRNA level is low to be detected while cattle have relatively high levels of OT mRNA in their testes [4]. OTR distribution characteristics are similar to the OT. The OT receptors were localized in the testis of the rats [4]. However, in the tammar wallaby, the mesotocin receptor gene and protein, which are highly homologous to the OT receptor, are not expressed in the testis, but in the prostate gland [5].

OT in the male reproductive system is not limited to the testis, the paracrine mode has high similarity with the OT secretion style in female reproductive tissues. Significant amounts of the peptide can be detected in the prostate and epididymis [6]. In the human, OT appears to exist in testis, epididymis, and prostate.

Testicular OT may have a role to play in the reproductive processes of the male by influencing the production of gonadal steroids. OT was found to stimulate testosterone production in mice [7], as well as in goats and pre-pubertal rats [8, 9]. In cell experiments of rat Leydig cells, OT also has the foundation to stimulate testosterone production [10]. But this effect remains controversial. In other purified Leydig cells research, no significant effect was observed [11]. Meanwhile, as well known, testosterone is an important agonist of ejaculation. So, OT may play an indirect role in the physiological process of male reproduction by gonadal steroids, especially testosterone.

What's more, the crosstalk between OT and vasopressin is also worthy of attention. In different species [12], the crosstalk phenomenon has been found [12]. Current research findings suggest that the affinity of OT to both OTR and vasopressin receptors is similar whereas OT has a higher affinity to its receptor than to vasopressin receptors. Vasopressin might also have an important effect on OT-mediated contractility in human myometrium and the ejaculation related tissues (prostatic urethra, bladder neck, and ejaculatory duct) of rats and rabbits [13].

Nevertheless, the classic roles of both peptides are still preserved; where OT is associated with contractile effects in both genders (ejaculation in men and uterus contraction in women) and social behaviors whereas vasopressin is closely related to water homeostasis and blood pressure regulation. OT acting through AVP-receptors and its receptor, which may explain some observed OT side effects, like headache and dizziness. This interaction between OT and vasopressin may also explain why vasopressin while showing similar contractibility to OT in the male reproductive tract, may also cause more severe side effects on the kidneys and cardiovascular system.

2.2 Female reproductive tissues

One of OT's traditional target is the pregnant uterus. In rats, the OT gene was found to be expressed in the rat uterine epithelium, amnion, and placenta [14, 15] and humans in amnion, chorion, decidua, and placenta [16]. According to this study result, OT gene expression in chorio-decidual issues was found to have increased three- to fourfold around the time of labor onset [16]. Another research finding also demonstrated that rat uterus OT mRNA increased more than 150-fold at term [14].

However, in maternal plasma, the prominent rise of OT before the onset of labor was not detected in most studies. Besides, the transcriptional level and transcripts of the OT gene are different across organs. Chibbar et.al [16] found that transcriptional levels are highest in the decidua, less in the chorion, and lowest in the placenta. The transcript size in amnion and chorion is larger than the transcript size in the decidua.

There is a popular belief that OT synthesis in gestation is a paracrine system [17]. The known issues include the fetal membranes amnion, chorion and placenta, and the maternal decidua. The location of OT synthesis is parallel with the place where OT gene expression takes place. These OT synthesized by these issues may be the source of OT in amniotic fluid. Possibly, the OT secreted in the form of paracrine is the main source of OT binding with myometrium OTR. This paracrine system was also found in rabbits and bovine [18, 19]. In the pregnant cow, during the whole pregnancy, OT mRNA levels were very low in uterine tissues and appeared to be upregulated at term. Moreover, OT was also found to be synthesized in the corpus luteum. Particularly, after the onset of labor, both OT gene expression and OT peptide are at significant levels in the corpus luteum [18].

Due to the upregulation of OT receptor gene transcription levels and a dramatic rise in OT receptor concentrations in uterine myometrium, uterine sensitivity to OT overtly increases in late pregnancy [14]. The phenomenon is demonstrated both in rat and in human species [15, 20]. It is worthy of noting that OT receptor mRNA expresses highest in the myometrium, low in decidua and chorion, and not detected in the placenta [20], which is in line with the OT gene transcriptional characteristics. Besides, the concentration of oxytocin receptors in the myometrium reaches maximum levels in early labor but in the decidua, the concentration is at peak (nearly five-fold) at parturition [21, 22]. The high concentration of OT receptors in myometrium is relevant to uterine contractility. After parturition, the concentrations of OT receptors decline at a rapid pace. In rats, the uterine OT receptor mRNA levels decreased more than seven-fold within 24 h [23]. The decrease of the OT receptors may be associated with avoiding unnecessary uterus contractility during lactation when maternal OT levels are raised.

Steroid hormones have been proved to be important mediators of OT secretion and OTR gene expression. In 1993, Broad et al. [24] demonstrated that pregnant sheep exposed to progesterone had more OT mRNA in the paraventricular and supraoptic nuclei of the hypothalamus, while those exposed to estrogen didn't show significant growth in the supraoptic nuclei. However, testosterone enhancement during pregnancy brought about decreased oxytocin mRNA expression in the paraventricular nuclei of pregnant rats [25]. Estrogen and testosterone may play an opposite role in the central OT system. While in the peripheral system, estrogens were found to be a strong inductive agent of uterine OT gene expression in the rat uterine, which is seven-fold stronger than progesterone administration [23].

Other hormones also affect the OT. Prostaglandin (PG), essential for parturition, is one of the mediator hormones. Apart from inducing contractions, oxytocin also stimulates prostaglandin synthesis through receptors in the decidua [26]. OT can stimulate the synthesis of PG in the decidua, not in the myometrium *in vitro* [21]. Prostaglandins themselves continue to further uterine contractions, soften the cervix, induce gap-junctions, and intensify the myometrium's sensitivity for oxytocin. At the end of the first stage of labor, the membranes usually rupture leading to a further increase in prostaglandin synthesis, so that once the mechanism is started, it can no longer be interrupted. And OT is a potent stimulator of prostaglandin E_2 synthesis of rabbit amnion cells [27]. According to the study of Gross et.al [28], mice with cyclooxygenase-1 (COX-1), required for the major synthesis of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), deficiency demonstrated impaired luteolysis, as proved by high

serum progesterone concentration and ovarian histology in late pregnancy, as well as delayed induction of uterine oxytocin receptors. Surprisingly, mice deficient in both OT and COX-1 continued to start labor at a normal time. The possible reason for the experiment phenomenon is the opposite effect on the determination of the onset of murine labor-elevated $PGF_{2\alpha}$ production may overcome the luteotrophic action of oxytocin in late gestation. Besides, there may be a crosstalk between OTR and PG receptor [29], because the OTR antagonists not only inhibit OTR but also PG receptors. In summary, OT and its receptors may be regulated by many other hormones, so the interaction between them cannot be ignored in future studies.

3. Oxytocin and behavioral effects

3.1 Maternal behavior

3.1.1 Animal studies

Oxytocin and oxytocin receptors are essential for maternal studies [17, 30, 31]. In oxytocin receptor knockout mice, $Oxtr^{-/-}$ and $Oxtr^{FB/FB}$ mice show largely normal maternal behavior. But it is worth mention that with external disturbance ruled out, $Oxtr^{FB/FB}$ female mice's pups mortality increases compared to wildtype females'. And the possible reasons for the higher mortality are unclear [32]. Interestingly, during maternal retrieval behaviors, there is lateralization in oxytocin receptor expression in the female auditory cortex: more oxytocin receptors are expressed in the left auditory cortex compared to the right auditory cortex in mothers [33].

Most scientific studies suggest that oxytocin is critical to the onset and maintenance of maternal behavior [34]. However, recent research finding of oxytocin receptor gene knockout mice indicates that oxytocin can lower the threshold for the initiation of maternal behavior, however, once the program is started, oxytocin is not crucial to its maintenance [35].

The most recognized understanding of the modification mechanism is the OT-dopamine system: OT circuits interact closely with dopaminergic circuits to mediate maternal behavior. In one research, direct infusion of oxytocin into the ventral tegmental area has been proved to increase the dopamine signal in the nucleus accumbens. Besides, compared with low pup licking/grooming (LG) mothers, high LG mothers show a greater rise in dopamine signal during pup LG behavior, and this alteration diminished with infusions of an oxytocin receptor antagonist directly into the VTA [36]. Studies on OT-related maternal function mechanisms need to expand.

3.1.2 Human studies

Animal research has demonstrated that maternal care behavior pattern varies as the alternation of peripheral OT level across species including sheep [30], monkeys, and rats [31]. Now, many important advances have been extended from animal models to humans, illustrating the role of OT in human mothering behavior. Research in this area has revealed that many factors could result in the individual differences of OT secretion and OT-related functions in women.

Mother-infant attachment is the first important factor. In a control experiment [37], fifty mothers and their 7-month-old infants were divided into two pattern groups: maternal gaze group and maternal gaze toward and gaze shifts away from the infant group, mother's oxytocin response shows a positive correlation with

duration of time gaze on her infant and a negative correlation with the frequency of gaze shift from infants. Breastfeeding is another crucial part of mother-infant attachment. There is a research finding that indicates breastfeeding mothers show higher maternal sensitivity when listening to their infants crying compared to formula-feeding in the early postpartum [38]. And other academic study results are consistent with the understanding that mother-infant interaction enhances maternal oxytocin response [39]. Moreover, early caregiving experiences also influence the OT system. Women's levels of CSF OT are positively correlated with the severity and duration of abuse and neglect to which they were exposed in childhood [40]. In females without harsh parenting experiences, the mother's handgrip force (which may be related to sensitive caregiving behavior) decreases in response to infant crying after they intake intranasal oxytocin [41].

Studies also have examined OT-related maternal brain responses. Strathearn et al. discovered that dopamine-associated reward regions, as well as the hypothalamic OT regions, were activated when mothers with secure attachment viewed their infants smiling or crying images [42]. Similar results were reported by Atzil et al. who demonstrated that mothers who displayed synchronous forms of mothering showed activation of the nucleus accumbens, a key reward region while viewing video clips of their infants. Notably, activations in these brain regions were correlated with the peripheral measures of OT in these mothers.

3.2 Mating

OT in human reproduction is involved in both central and peripheral levels. During orgasm, OT acts on the contractions of male and female internal reproductive organs. To the male, OT receptors are linked with semen emission [1], while as to the female, OT receptors within the uterus contribute to uterine contractions. Previous scientific research on the role of OT in human reproduction is mainly concentrated on the periphery. Many studies have proved a prominent increase in plasma OT levels during sexual arousal and immediately the following orgasm in both men and women [43, 44]. However, with the development of neuroimaging techniques, like functional magnetic resonance imaging studies (fMRI) and positron emission tomography (PET), the focus mostly transfers into OT's central effects. To date, many brain areas such as the anterior lobe of the cerebellar vermis and deep cerebellar nuclei respond actively during orgasm [45].

3.2.1 Central OT

For its convivence and intuition, fMRI scanning and PET have become essential tools for research into how central systems regulate human reproduction. As important sexually dimorphic brain regions, the thalamus and hypothalamus play a crucial role in sexual arousal and sexual behavior [46]. During orgasm, women's brain areas included the hypothalamic paraventricular nucleus (PVN)-a major site of OT production and secretion and the periaqueductal gray which receives projections from the PVN show significant activation. Many other brain regions also show activation in mating, such as the medial amygdala, anterior cingulate, nucleus tractus solitarii (NTS), and cerebellar (the anterior lobe of the cerebellar vermis and deep cerebellar nuclei) [45, 46]. However, the association between the activatory regions and the OT system still requires further elucidation.

There is an obvious gender difference in sexual behavior, especially in mating. According to an fMRI study using 20 female and 20 male healthy subjects, when viewing erotic film excerpts, male subjects experience greater sexual arousal (SA).

By analyzing fMRI data, compared with female subjects, male subjects show greater hypothalamic activation, Karama et al. [46] speculate the gender difference may be correlated with activation of the hypothalamus- a brain region that plays an important role in sexual behavior. Other studies involving male subjects also found similar activation of this brain area during erotic visual stimulation [47, 48]. Interestingly, the hypothalamus supraoptic nucleus (SON) and PVN are the main sites of OT gene expression. Besides, only the periaqueductal gray in man where OT was released into prominently activated during orgasm [45].

In summary, there may be some connection between OT and sexual behavior, but the specific mechanism is unclear. Future studies may pay more attention to link brain activation with behavioral effects to figure out the function of central OT in human sexuality. It's worth noting that, although females' hypothalamus activation is interior to males', peripheral OT in both genders shows similarities during sexual arousal.

3.2.2 Peripheral OT

Researchers have attempted to link peripheral OT with reproductive tissues. According to the above, OT receptors within epithelial cells of the epididymis facilitate contractions during ejaculation, contributing to semen emission. These receptors may mediate sperm production as well. In the female, OT receptors exist in the uterus, appearing in higher concentrations during labor. Besides, during the female orgasm, contractions also occur for the activation of OT receptors in the non-pregnant uterus [49]. The role of these contractions is popularly accepted as facilitating sperm transport (often referred to as the "upsuck hypothesis"). A study of 50 women conducted by Wildt et al. [50] supported this hypothesis. Following intravenous OT injection during the follicular stage, a larger number of radiolabeled particles reached the oviduct that contained the dominant follicle, as well as the elevated amplitude of uterine contractions. It is obvious that OT is concerned with human uterine contractions; however, the purpose of these contractions during mating is not clear. It may be responsible for an arousal state in both sexes with exogenous OT exposure.

4. Clinical use of oxytocin

4.1 Autism spectrum disorders

OT has been put into clinical use concerning autism spectrum disorders (ASD). It is important to establish the appropriate dosage that should be given to humans. In a randomized placebo-controlled double-blind crossover trial which is aimed to inquire into OT's dose-dependent effects of a single oxytocin administration in autism, 17 male adults with ASD received 8 international units (IU) oxytocin, 24 IU or placebo before they proceeded four social-cognitive tasks and evaluate the effect of treatment by the measure of overt emotion salience [51]. The research finding suggests that just a low dose of oxytocin can modulate overt emotion salience.

OT's treatment effect works by enhancing brain activity. Under social stimulation, OT selectively improves the brain activity of key areas associated with attention and emotion regulation like the amygdala, hippocampus, mid-orbitofrontal cortex, and insula region [52]. And in another clinical trial, inducing oxytocin can restore brain activity of the medial prefrontal cortex [53].

4.2 Labor induction

OT is a highly efficient and safe agent for the induction the labor and has considerable therapeutic uses. Hofbauer, who first used oxytocin to induce labor, said, "with its power of producing regular, rhythmical and forcible uterine contractions, should be regarded as a most beneficent and valuable agent, which, however, should always be employed with the care of its limitations and dangers." Large-dose OT used in labor induction led to minimal, but not trivial, antidiuretic, and vascular activity [54], which may be associated with the vasopressin and prostaglandin. OT should be used in the lowest possible doses which can induce an effective clinical response.

Patients' resistance to induction or augmentation of labor caused by long-time use of OT in labor induction is not uncommon in the clinical. Daniel-Speigel et al. addressed this issue in a prospective, randomized trial of 104 women who received oxytocin via a low-dose protocol for labor induction. One group of women received intravenous oxytocin until 5-cm dilation, at which time it was discontinued, whereas the other group was continued on the dose of oxytocin that they were receiving at 5-cm dilation. They failed to show any significant difference between groups in the time interval from induction to the active phase, length of the active phase, or length of the second stage of labor. They concluded that continuing oxytocin infusion after the onset of active labor did not seem to have any benefit on the course of labor. In fact, women who received continuous oxytocin infusion throughout their labor course experienced greater rates of uterine hyperstimulation and underwent more cesarean sections. In our practice, we have found that if during induction of labor a high dose of oxytocin has been reached and maintained for a prolonged period and membranes are intact, it is sometimes beneficial to stop the infusion, let the patient rest for several hours, and then begin again. More uterine contractions were induced with each mU of oxytocin infused via pulsatile administration in comparison to using continuous infusion [55]. Different methods of OT infusion may result in discrepancies in labor induction. In patients with prelabor rupture of membranes, a Foley catheter with OT does not shorten the time to delivery compared with OT alone but may contribute to the increase in the chance of intraamniotic infection [56]. Pulsatile administration can prominently reduce the dose of OT required to induce labor [55].

According to the known OT physiological effects, highly specific OT antagonists may be of great therapeutic value for the prevention of preterm labor [57, 58]. To date, many OT antagonists have been developed, the relatively efficient of which is a drug called Retosiban. Retosiban is above 15 times more potent than atosiban which is a marketed intravenous OT antagonist at the human oxytocin receptor, as evidenced by effective inhibition of uterus contractions by intravenous and by oral administration in rats [59]. Moreover, antagonists of OT can also be used to treat dysmenorrhea by relaxing the uterine myometrium [60].

5. Summary

The link between OT oxytocin and pregnancy is explored in three aspects: physiology, ethology, and clinical application. A conclusion can be drawn from the above: the link between OT and pregnancy appears to be strong, both in the first and second trimesters, especially in the third trimester. Although most of the OT mechanisms and effects are known, there are still some suspects, for example, what's the function of the contraction caused by OT during orgasm. Additionally,

whether the OT synthesized in different parts can be transported to other parts to do their job? And if so, how do they communicate? Apart from the classical effect, in recent years, the role of oxytocin in behavior has received increasing attention. OT disorder is related to behavioral disorders like childhood cognitive impairment, ASD, and maternal postpartum depression [61], but as far as the scientific research is concerned, the mechanism of this phenomenon is not very specific. And as such, to explain this phenomenon, more efforts are needed in the future. Last but not least, although OT has rare side effects on the human body, it is still worth discussing how to use OT safely and efficiently in clinical practice. In conclusion, OT is essential for pregnancy, and more detailed function mechanism should be explored in future research.

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