The physiology and pharmacology of oxytocin in labor and in the peripartum period

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Oxytocin is a reproductive hormone implicated in the process of parturition and widely used during labor. Oxytocin is produced within the supraoptic nucleus and paraventricular nucleus of the hypothalamus and released from the posterior pituitary lobe into the circulation. Oxytocin is released in pulses with increasing frequency and amplitude in the first and second stages of labor, with a few pulses released in the third stage of labor. During labor, the fetus exerts pressure on the cervix of the uterus, which activates a feedforward reflex—the Ferguson reflex—which releases oxytocin. When myometrial contractions activate sympathetic nerves, it decreases oxytocin release. When oxytocin binds to specific myometrial oxytocin receptors, it induces myometrial contractions. High levels of circulating estrogen at term make the receptors more sensitive. In addition, oxytocin stimulates prostaglandin synthesis and release in the decidua and chorioamniotic membranes by activating a specific type of oxytocin receptor. Prostaglandins contribute to cervical ripening and uterine contractility in labor. The oxytocin system in the brain has been implicated in decreasing maternal levels of fear, pain, and stress, and oxytocin release and function during labor are stimulated by a social support. Moreover, studies suggest, but have not yet proven, that labor may be associated with long-term, behavioral and physiological adaptations in the mother and infant, possibly involving epigenetic modulation of oxytocin production and release and the oxytocin receptor. In addition, infusions of synthetic oxytocin are used to induce and augment labor. Oxytocin may be administered according to different dose regimens at increasing rates from 1 to 3 mIU/min to a maximal rate of 36 mIU/min at 15- to 40-minute intervals. The total amount of synthetic oxytocin given during labor can be 5 to 10 IU, but lower and higher amounts of oxytocin may also be given. High-dose infusions of oxytocin may shorten the duration of labor by up to 2 hours compared with no infusion of oxytocin; however, it does not lower the frequency of cesarean delivery.

When synthetic oxytocin is administered, the plasma concentration of oxytocin increases in a dose-dependent way: at infusion rates of 20 to 30 mIU/min, plasma oxytocin concentration increases approximately 2- to 3-fold above the basal level. Synthetic oxytocin administered at recommended dose levels is not likely to cross the placenta or maternal blood-brain barrier. Synthetic oxytocin should be administered with caution as high levels may induce tachystole and uterine overstimulation, with potentially negative consequences for the fetus and possibly the mother. Of note, 5 to 10 IU of synthetic oxytocin is often routinely given as an intravenous or intramuscular bolus administration after delivery to induce uterine contractility, which, in turn, induces uterine separation of the placenta and prevents postpartum hemorrhage. Furthermore, it promotes the expulsion of the placenta.

Key words: augmentation, birth, epigenetic changes, Ferguson reflex, first stage, induction, infusion of oxytocin, labor, myometrial contractions, oxytocin, plasma levels, pregnancy, prostaglandins, pulsatile secretion, receptor, second stage, synthetic oxytocin, third stage

Introduction

In 1906, Sir Henry Dale reported that extracts of the posterior pituitary lobe promoted uterine contractions in cats. He called the substance "oxytocin," which is Greek for "rapid birth."[3] In addition, pituitary extracts induced milk ejection.[4,5] Half a century later, Vincent Du Vigneaud sequenced oxytocin from isolated bovine pituitary extracts. It corresponded to a cyclic pentapeptide containing cystine and a tripeptide (prolyl-leucyl-glycine) (Figure 1). Soon after, he synthesized oxytocin by adding the individual amino acids to each other, which allowed clinicians to use it.[6,7]

Oxytocin is produced in neurons of the supraoptic nucleus (SON) and paraventricular nucleus (PVN) of the hypothalamus and released into the circulation from the posterior pituitary lobe. It induces contractions of the uterus and the myoepithelial cells in the mammary gland during birth and lactation. Furthermore, these same neurons from the SON and PVN project to important regulatory areas within the brain. A plethora of centrally induced, oxytocin-linked, behavioral and physiological effects are induced concerning labor[8] and breastfeeding.[9,10] In addition, locally produced oxytocin within the decidua and chorioamniotic membranes stimulates the production of prostaglandins.[11–14] All oxytocin effects are mediated by the oxytocin receptor through different intracellular mechanisms.[15–17]

Oxytocin is a reproductive hormone in a broad sense. Concerning its role in labor and breastfeeding, oxytocin

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Received Oct. 12, 2022; revised April 5, 2023; accepted April 9, 2023.

Kerstin Uvnäs Moberg owns shares in a company called Oxagon AB, in which the effects of locally applied oxytocin on vaginal atrophy in menopausal women is studied.

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0002-9378

https://doi.org/10.1016/j.ajog.2023.04.011

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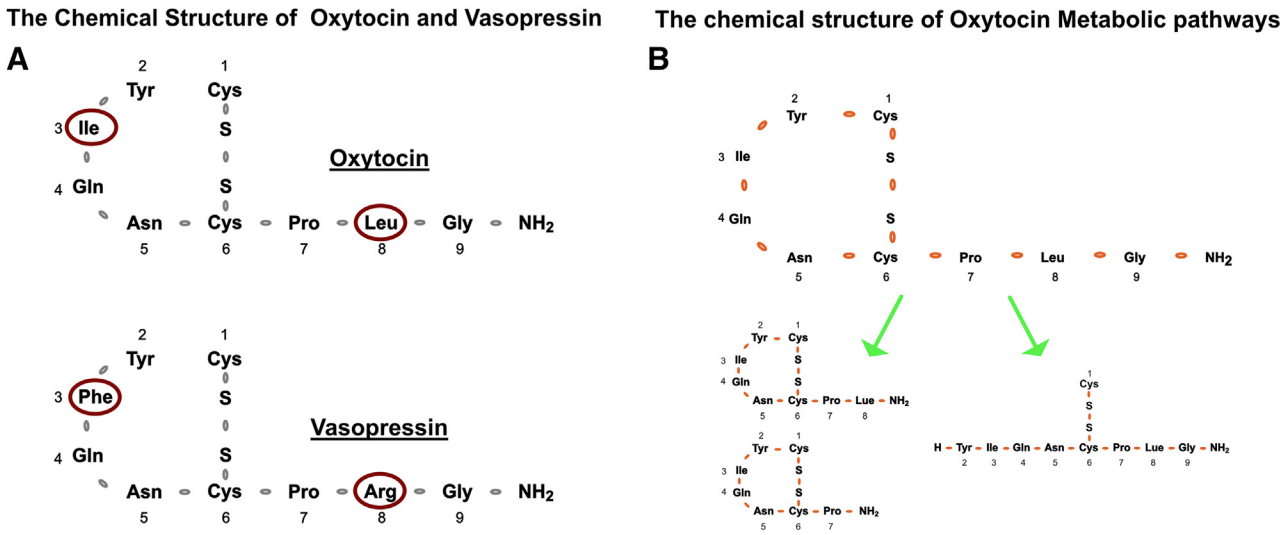
FIGURE 1
Chemical structure of oxytocin, vasopressin and oxytocin metabolites



A, The figure shows the chemical structure of the oxytocin and vasopressin molecules. Oxytocin consists of a cyclic structure with 6 amino acids (cysteine, tyrosine, isoleucine, glutamine, asparagine, and cysteine) and a linear structure with 3 amino acids (proline, leucine, and glycine). Note that the 2 cysteines are linked together by a disulfide bond and that the glycine at the carboxy or C-terminal end of the molecule is amidated. In vasopressin, the amino acids isoleucine and leucine are exchanged by phenylalanine and arginine, respectively. **B,** The figure shows the main metabolic pathways by which oxytocin is degraded. As shown by the left pathway, one or several amino acids can be split off from the C-terminal end of the molecule. As shown by the right pathway, the cyclic structure of the oxytocin molecule can be opened up, for example, between the amino acids cysteine and tyrosine, to create linear forms of the oxytocin molecule. The linear oxytocin molecule can be further degraded to shorter fragments by amino acids being split off from both the amino and C-terminal ends of the molecule. In addition, a cysteine molecule may be split off from the linear molecule.

C-terminal, carboxy-terminal.

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stimulates the maturation of eggs in the follicles, tubal transport of the eggs, fertilization of eggs, implantation of the blastocyst, and stimulation of growth of the fetus,[18–23] Fritz Fuchs and Anne-Riita Fuchs contributed substantially to our understanding of the role of oxytocin in parturition. Their results help connect recently obtained knowledge regarding oxytocin-linked molecular mechanisms to physiological processes.

Synthetic oxytocin has been used for more than 60 years to induce and augment labor, to decrease the frequency of postpartum hemorrhage (PPH), and sometimes to stimulate milk ejection, such as when an infant is premature.[24,25] Currently, many birthing women receive infusions of synthetic oxytocin to induce or augment their labor. In addition, hospitals often give mothers a bolus administration of oxytocin after delivery.

This study aimed to review the function of oxytocin during labor, the differences between oxytocin in the plasma and oxytocin's functions as a neurohormone, and the use of synthetic oxytocin in inducing and augmenting labor.

Oxytocin

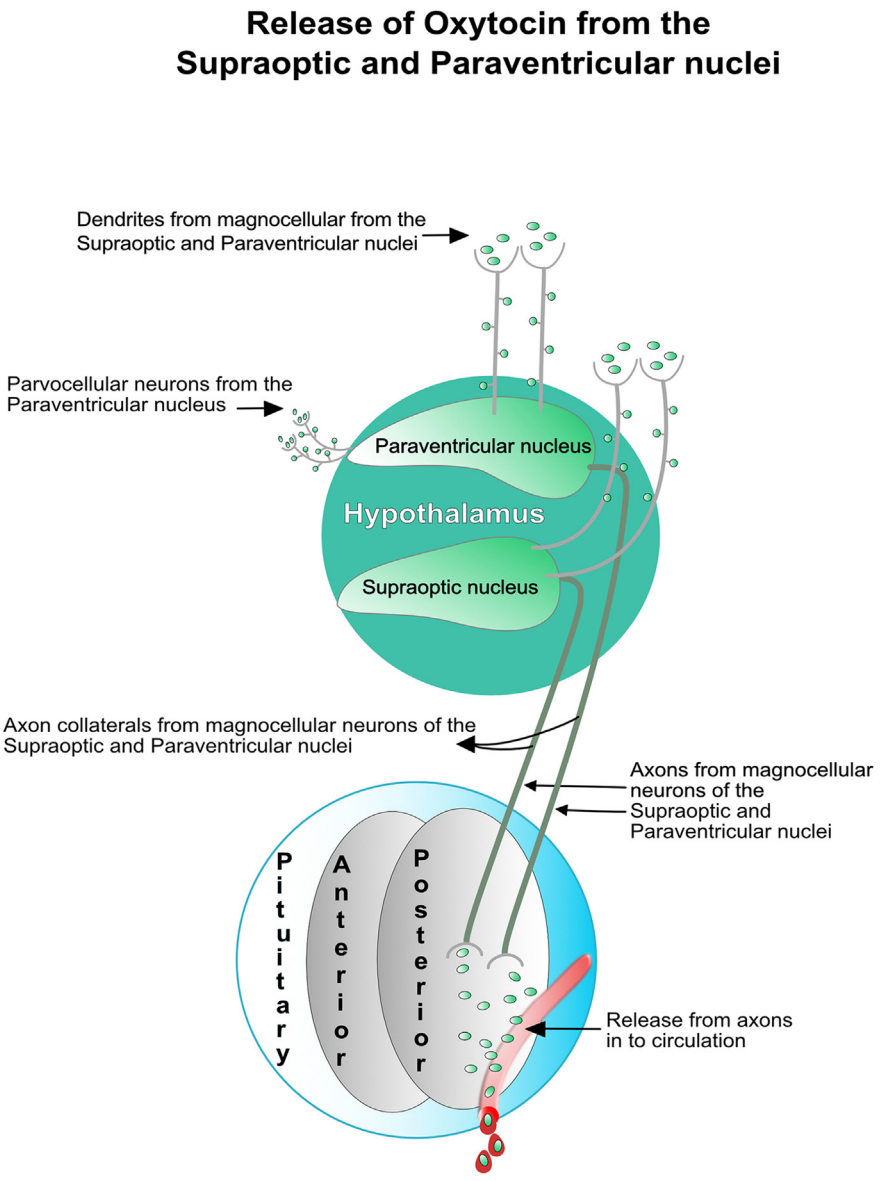
Oxytocin is produced at multiple sites and induces many different effects via several mechanisms of action. Because oxytocin receptors are widely distributed, it makes more sense to refer to an oxytocin system rather than to oxytocin.[10,26]

Structure of the oxytocin system

Oxytocin is mainly produced in the magnocellular neurons of the SON and PVN of the hypothalamus[15] and is transported via axons to the posterior pituitary lobe, from where it is released into the circulation to act as a classical hormone during labor, delivery, and breastfeeding.[8–10,15] Moreover, it influences brain function via local mechanisms.[27] A multitude of separately organized bundles of parvocellular neurons from the PVN project to important regulatory areas in the brain, where oxytocin influences behavioral and physiological functions.[28–30] In addition, magnocellular oxytocin neurons projecting to the posterior pituitary send axon collaterals to various brain areas, including the median eminence, amygdala, hippocampus, cingulate, and frontal cortex.[31,32] In this way, oxytocin induces different integrated effects consisting of various combinations of circulating oxytocin-mediated effects and centrally induced behavioral and physiological functions (Figure 2).[33,34]

In addition, oxytocin is produced in the peripheral organs, such as the cardiovascular system; in the gastrointestinal tract, ovaries, decidua of the uterus,

FIGURE 2
Release of oxytocin from the supraoptic and paraventricular nuclei



Oxytocin from magnocellular neurons from the SON and PVN is transported via axons of the oxytocin neurons to the posterior pituitary, where it is released into the circulation. Oxytocin from the magnocellular neurons of the SON and PVN is released from dendrites of the oxytocin neurons into the surrounding brain tissue, where it reaches neighboring areas in the brain by diffusion. Oxytocin is released into many areas of the brain from axon collaterals emanating from the axons of the magnocellular neurons from the SON and PVN, projecting to the posterior pituitary. The axon collaterals project to several brain regions, including the median eminence and anterior pituitary, amygdala, and cortex. Oxytocin is released from parvocellular neurons from the PVN into many regulatory areas in the brain. The figure illustrates how oxytocin released from the same oxytocin neurons may simultaneously be released into the circulation to stimulate uterine contractions and into the brain to influence brain function.

PVN, paraventricular nucleus; *SON*, supraoptic nucleus.

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and chorioamniotic membranes; and in cells, such as endothelial cells and keratinocytes.[11,12,15,35] Peripherally produced oxytocin mainly exerts local, modulatory functions via paracrine mechanisms.[15]

Effects of oxytocin

The classical effects of oxytocin include stimulating contractions of the myometrium and myoepithelial cells in the mammary glands.[3,4,8–10] In addition, many new effects of oxytocin have been identified. Oxytocin stimulates social interactive behaviors, including caregiving and maternal defense of the offspring[2,8,10,36–38] It decreases fear, pain, and inflammation and decreases stress levels by down-regulation of the hypothalamic-pituitary axis and sympathetic nervous system.[33,39–42] In addition, it increases parasympathetic and vagal nerve activities, which promote absorption, digestion, and metabolism of ingested food.[9,10,33,41] Furthermore, oxytocin exerts healing and restorative effects and stimulates wound healing.[43] Moreover, it may stimulate the growth of stem cells[44] and regenerate skeletal muscle by stimulating the activity of stem cells in muscle tissue.[45] In women experiencing menopause, the atrophic uterine mucosa consists of 2 to 3 layers of cells. Local intravaginal application of oxytocin increases the number of cell layers to 12 to 14, which is seen in fertile women.[46,47] The chemically related substance vasopressin is involved in the regulation of behavioral and physiological functions, but the effect profile is more linked to aggression and increased stress levels.[48]

Molecular structure

The oxytocin molecule is a nonapeptide that consists of a ring of 6 amino acids, kept together by a disulfide bridge, with a 3-amino acid long tail with an amidated glycine residue in the carboxy-terminal (C-terminal) end (Figure 1, A). The oxytocin molecule differs from vasopressin by only 2 amino acids at positions 3 and 8 (Figure 1, A). The structure of oxytocin is similar in all

mammals, indicating that the molecule is well conserved. In addition, oxytocinlike peptides occur in birds and fish, "mesotocin" and "isotocin." respectively, and these peptides are linked to egg laying and sociosexual behaviors. Moreover, oxytocin- and vasopressinlike peptides are produced in more primitive animals and have been shown to participate in reproductive behaviors and egg laying.[17]

Synthesis and metabolism of oxytocin

Similar to all peptide hormones, oxytocin derives from a much larger prohormone, including neurophysin. Enzymatic processes degrade the prohormone into smaller molecules. Longer prohormones of oxytocin have been demonstrated, especially in early life.[15] Molecules that are not completely degraded to oxytocin but are extended at the carboxyl end of the molecule are involved in cardiac differentiation. Moreover, they stimulate heart cell growth and stimulate growth in a more general sense.[49] Examples of these molecules include oxytocin-glycine-lysine-arginine, oxytocin-glycine-lysine and oxytocin-glycine, and C-terminally extended molecules. An extended oxytocin molecule is likely released into the circulation, in response to certain stimuli, such as high concentrations of estrogens during pregnancy.[15,50]

The brain and periphery both produce active fragments or metabolites of oxytocin, which may exert behavioral and physiological actions corresponding to those induced by the principal hormone, oxytocin. Oxytocin is degraded by oxytocinases in 2 principal ways: by opening of the ring, thereby giving rise to a linear variant of oxytocin, and by deletion of single amino acids from the amino- and C-terminal ends of the oxytocin molecule by amino- or carboxypeptidases. In this way, several cyclic and linear variants of the molecule are formed (Figure 1, B).[15] The intact ring structure is necessary for the contractile effects of oxytocin, but the effect is weakened as amino acids in the tail (prol-leu-gly) are lost.[15] Linear oxytocin fragments with an intact C-terminal, such as oxytocin 1-9 or 4-9, influence memory and give rise to calm, antistress, and restorative effects.[51,52] Furthermore, the sequence prol-leu-gly is known as a melanocyte-inhibiting factor (MIF) and has been shown to have antidepressant effects.[53] Oxytocin, being the principal hormone, can give rise to all of these effects.[15,51]

The release rate of endogenous oxytocin (or the administration of synthetic oxytocin) and the speed by which the oxytocin molecule is degraded determine the level of oxytocin in the circulation or in other tissues. The degradation of oxytocin takes place in the liver, kidneys, and any peripheral organ and in the circulation.[15] The half-life of oxytocin seems to be relatively short: 3 to 6 minutes.[54] However, it may be as long as 30 to 40 minutes. Studies of intravenous oxytocin administration have demonstrated a 2-compartment model for oxytocin elimination.[55]

Circulating oxytocinases increase 10-fold in the late term of pregnancy and during labor because the placenta produces placental leucine-amino-peptidase, a specific type of oxytocinase. The increased degradation of oxytocin during labor and birth suggests that the half-life of oxytocin might be shortened during these periods. Surprisingly, few conclusive studies measure oxytocin half-life concerning labor. However, it took 3 times as much synthetic oxytocin to induce the same plasma level of oxytocin in late pregnancy compared with the same women at 6 to 8 weeks after delivery.[56–58] As a hydrophilic and polar peptide molecule (molecular weight of 1007), oxytocin is not supposed to cross biological membranes easily, such as the blood-brain barrier. Less than 1% of an administered dose of synthetic oxytocin passes into the brain.[59]

The oxytocin gene

The oxytocin and vasopressin genes are located on the human chromosome 20p13. The structure of the oxytocin and vasopressin genes and the post-translational modifications of the 2 peptides are very similar, supporting the assumption that they have developed from a common ancestral gene.[15] The function of the oxytocin gene can be enhanced via effects in the promoter region of the gene via estrogen-alpha and estrogen-beta receptors, thyroid alpha receptors, and retinoic acid alpha and beta receptors.[15]

The oxytocin receptor

Localization

Oxytocin receptors, which mediate the effects of oxytocin, are present in the myometrium and myoepithelial cells of the mammary glands and in many peripheral tissues, such as the heart, blood vessels, kidney, ovary, testis, and thymus; adipose tissues; deciduae; and chorioamniotic membranes.[10,15–17,60–62] In addition, oxytocin receptors are found in many areas of the brain, including the olfactory system, limbic system, hypothalamus, basal ganglia, brain stem, spinal cord, and some cortical regions.[17]

Structure of the oxytocin receptor

The oxytocin receptor, such as the closely related vasopressin receptor, belongs to the G-protein–type receptor, which transfers information from the cell membrane into the cell via G proteins. Only 1 oxytocin receptor has been demonstrated, whereas 3 different vasopressin receptors exist (V1a, V1b, and V2 receptors). The oxytocin receptor contains 389 amino acids and is a 7-transmembrane helix receptor with 3 extracellular and 3 intracellular loops. The extracellular loops are of great importance for the binding of oxytocin to its receptor (Figure 3).[16,17]

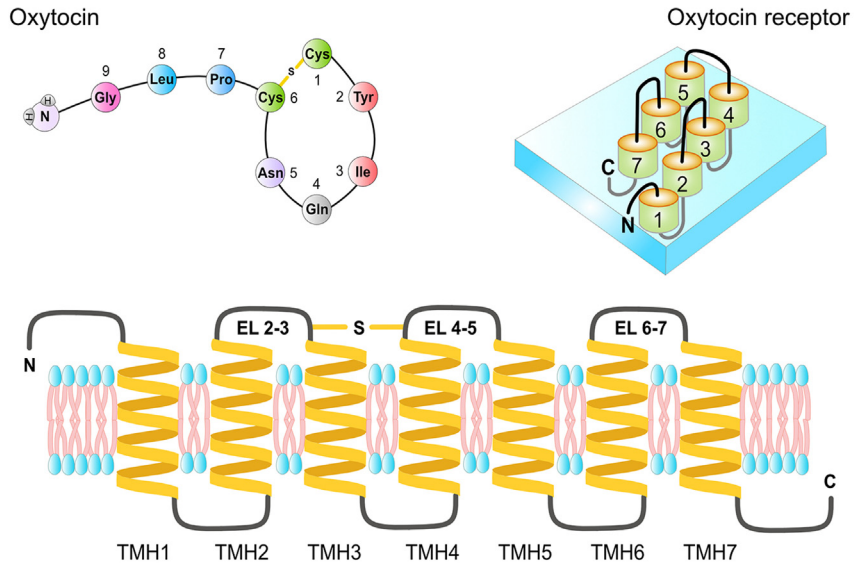
The oxytocin and oxytocin receptor complex

The oxytocin receptor is coupled to a trimeric complex of G proteins, consisting of 1 G alpha unit and 1 beta or gamma unit. Several different subforms of the proteins exist, which contribute to different compositions of the G-protein complex. These structural differences, in part, explain why different effects may be induced when oxytocin binds to its receptor.[15,17]

Molecular pathways activated in response to binding between oxytocin and its receptor

When oxytocin binds to its receptor, multiple intracellular effects are induced, the effect spectrum, in part, being

FIGURE 3
Illustration of the binding between oxytocin and its receptor



The figure shows the structure of the oxytocin molecule and oxytocin receptor and a 3-dimensional illustration of the oxytocin receptor within the cell membrane. The oxytocin receptor contains 389 amino acids and is a 7-transmembrane helix receptor (TMH1-7) with 3 extracellular (EL 2-3, EL 4-5, and EL 6-7) and 3 intracellular loops. The extracellular loops are of great importance for binding of oxytocin to its receptor. The figure is redrawn from a freely available figure published in a paper by Jurek and Neumann.[17]

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dependent on the type of cell that is activated. Most experimental studies have been performed on myometrial cells. In this model, when oxytocin binds to its receptor, the beta or gamma unit is separated from the G-alpha protein. This, in turn, leads to the stimulation of phospholipase-C. This enzyme catalyzes phosphatidylinositol 4,5-bisphosphate breakdown to diacylglycerol and inositol 1,4,5, triphosphate and triggers calcium (Ca^{++}) release from the smooth endoplasmic reticulum. This Ca^{++} activates calmodulin, leading to the phosphorylation of myosin light-chain kinase that phosphorylates myosin light chains, which, in turn, facilitates actin-myosin interaction and contraction. During labor, the frequency of Ca^{++} oscillations in the myometrial cells is linked to the amount of oxytocin-induced contractions (Figure 4).

In contrast, in myometrial cells isolated from pregnant rats, oxytocin receptor binding stimulates adenylyl cyclase 2, which suppresses Ca^{++} and reduces contractions. These data demonstrate an inhibition of the oxytocin-induced contractile effects on myometrial cells during pregnancy, contributing to uterine quiescence during this period.[15–17]

In addition, intracellular pathways other than those leading to myometrial contractions may be activated in response to binding between oxytocin and its receptor. One of these pathways involves mitogen-activated protein kinase (MAPK) MEK 1-2 and ERK 1-2. By activation of this pathway, oxytocin has been shown to stimulate the growth of cardiomyocytes, stimulate osteoblasts, induce maturation of human mesenchymal stem cells, reverse osteoporosis, and improve muscle regeneration by enhancing muscle stem cell regeneration.[44,45,63] The synthesis of prostaglandins in the decidua and chorioamniotic membranes involves an oxytocin-induced activation of the MAPK/ERK pathway.[15–17]

During labor, the oxytocin receptor in the myometrium gives rise to myometrial contractions, whereas the oxytocin receptors in the decidua and chorioamniotic membranes are linked with the synthesis and secretion of prostaglandins and inflammatory substances, such as leukotrienes and arachidonic acid.[11–14] Although both these effects are mediated by oxytocin, they are linked to specific receptor populations, which activate different intracellular signaling pathways, as described above.[15–17]

The oxytocin receptor gene

There is only 1 gene coding for the expression of the oxytocin receptor, which is located on chromosome 3p25(A) in humans. The oxytocin receptor gene consists of 4 exons and 3 introns. Estrogen can bind to the promoter region of the oxytocin receptor gene via both estrogen alpha and estrogen beta receptors to activate transcription of the oxytocin receptor. Progesterone inhibits the transcription and translation of the oxytocin receptor gene, thereby leading to a relative quiescence of uterine smooth muscles and a low frequency of contractions during pregnancy.[15–17]

Factors that influence the function and availability of the oxytocin receptor

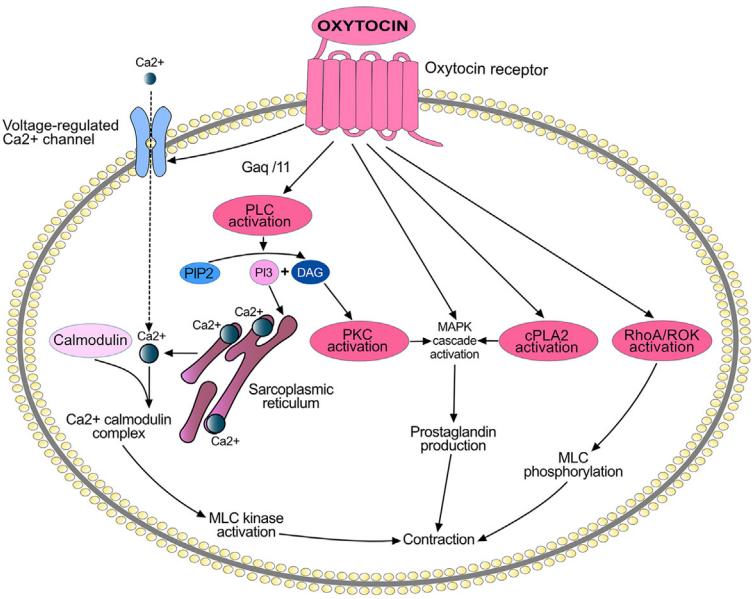
High- and low-affinity state of the oxytocin receptor

The oxytocin receptor may exist in 2 different affinity states: low affinity (Kd of >100 nM) and high affinity (Kd of <1 to 5 nM), which optimizes the physiological activity of oxytocin. The low-affinity state can transfer into the high-affinity state and vice versa; the presence of Mg^{++} or Mn^{++} transfers the low-affinity state into the high-affinity state. Cholesterol stabilizes the oxytocin receptor in a high-affinity state.[16,17]

Effects of estrogen

The amount of oxytocin receptors in the myometrium gradually increases during

FIGURE 4
Intracellular pathways activated when oxytocin binds to its receptor



Stimulation of the oxytocin receptor leads to stimulation of PLC. This enzyme catalyzes PIP2 breakdown to DAG and IP3 and triggers calcium (Ca^{++}) release from the smooth endoplasmic reticulum. Ca^{++} activates CaM, leading to phosphorylation of MLCK that phosphorylates myosin light chains, which, in turn, facilitates actin-myosin interaction and contraction. In addition, the MAPK cascade is activated, which stimulates prostaglandin production and muscle contraction.

CaM, calmodulin; *DAG*, diacylglycerol; *IP3*, inositol 1,4,5, triphosphate; *MAPK*, mitogen-activated protein kinase; *MLCK*, myosin light-chain kinase; *PIP2*, phosphatidylinositol 4,5-bisphosphate; *PLC*, phospholipase-C.

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pregnancy in response to the high levels of estrogens, and at term, there is a 100-fold increase in the concentration of oxytocin receptors, showing that the synthesis and number of oxytocin receptors are enhanced.[15,62] In addition, estrogen increases the concentration of oxytocin receptors in the decidua and chorioamniotic membranes.[11,12]

Oxytocin receptor internalization

When oxytocin binds to its receptor, it also activates a G-protein–coupled receptor kinase, allowing binding to beta-arrestin, which leads to oxytocin receptor internalization or desensitization. Beta-arrestin uncouples the oxytocin receptor from its G proteins, and in doing so, it allows the receptor to be internalized or incorporated into the cell.[15–17]

Receptor desensitization

The availability of high levels of ligands over longer periods can result in receptor down-regulation and thereby insensitivity to the ligand. There is limited evidence for this type of down-regulation happening with oxytocin receptors. However, chronic exposure to high amounts of intranasally administered oxytocin in mice decreased the number of oxytocin receptors.[15–17] A desensitization of oxytocin receptors, which reduces the function of the receptors, hypothetically might occur after augmentation of labor by infusions of synthetic oxytocin.[64–67]

Methylation of the oxytocin receptor gene

The production of oxytocin receptors depends on the level of methylation of the DNA in the promoter region of the receptor as DNA methylation in this region reduces the accessibility of the oxytocin receptor for transcriptional factors. The higher the levels of methylation, the lower the levels of oxytocin receptor messenger RNA (mRNA) and oxytocin receptor production. This mechanism has achieved much attention lately, and studies are being performed to determine whether DNA methylation of oxytocin or the oxytocin receptor occurs after delivery in human mothers and their neonates.[15–17,68]

Oxytocin during pregnancy, labor, and delivery

Oxytocin and its receptors increase during pregnancy in preparation for labor and delivery. During labor, peak levels of oxytocin are released into the circulation, which induces uterine contractions to allow the birth of the fetus. Immediately after delivery, peak levels of circulating oxytocin stimulate uterine contractions to expel the placenta and lower the risk of PPH. Moreover, oxytocin is released in response to breastfeeding to contract the myoepithelial cells of the mammary gland to promote milk ejection.[8–10,15] In addition to these classical contractile effects of circulating oxytocin, oxytocin released from neurons within the brain exerts important adaptative, physiological, and psychological effects. These effects have been reviewed below.

Methodological considerations regarding measurements of oxytocin levels

The gold standard for the analysis of oxytocin concentrations is the immunologic technique radioimmunoassay (RIA), which is a very specific and sensitive technique for oxytocin levels and gives rise to reproducible measurements. RIA can detect oxytocin levels within the picomolar range with great accuracy. The antibodies used in high-quality RIAs are well characterized and are often specific for the entire oxytocin molecule and do not detect linear fragments of oxytocin or cyclic fragments in which amino acids have been split off from the C-terminal end of the molecule (Figure 1, B). The different processes involved in RIA are well described, and plasma samples are always extracted before analysis to diminish unspecific

binding.[65–67] Most high-quality studies during pregnancy and labor have used RIA. More recently, a simpler immunologic technique without radioactivity, enzyme-linked immunosorbent assay (ELISA), has been developed and used for the analysis of oxytocin concentrations. If the plasma is extracted before analysis, and if the antibodies are well characterized and specific for the cyclic oxytocin molecule, high-quality results can be obtained with ELISA. Without extraction, very high oxytocin levels, and sometimes different effect patterns of oxytocin, are obtained with ELISA, which may be caused by the detection of unspecific material in the samples. Furthermore, if the antibodies are less well characterized, which is sometimes the case with ELISA, measurements may include the detection of fragments or metabolites of oxytocin, for example, linear fragments of oxytocin, which are not detected by RIA (Figure 1, B).[51,69–71]

Collection and handling of samples

Oxytocin is released in short pulses with different intervals during labor, and therefore, it is necessary to collect multiple repeated blood samples at short time intervals to be able to detect the pulses. In addition, the speed by which blood samples are collected is crucial and must be standardized. Studies in which RIAs have been used most often include data based on multiple, serial blood samples, which will allow visualization of the oxytocin pulses. In contrast, studies using ELISA are generally based on only a few blood samples, reducing the value of the studies.[8] In addition, blood samples must be kept cold, and plasma must be frozen immediately after collection. Enzyme inhibitors, such as aprotinin (Trasylol), must be added to the samples to avoid the degradation of oxytocin in the tubes.

Large amounts of placental oxytocinase (placental leucine aminopeptidase [P-LAP]) are produced in the placenta during late pregnancy and labor, and circulating levels of P-LAP increase substantially. This circulating oxytocinase may influence the half-life of oxytocin in vivo and may induce degradation of oxytocin even after the collection of blood samples. This increases the need for rigorous handling of blood samples collected during labor.[56,57]

Although RIA is a highly sensitive and specific method for the detection of oxytocin levels, it is an indirect method in the sense that the oxytocin values obtained are based on changes in the balance within an equilibrium reaction, involving binding between antibodies to oxytocin and iodinated oxytocin or oxytocin from the samples. Methods that directly quantify the number of oxytocin molecules, such as mass spectrometry, are being developed.

Pregnancy

Oxytocin concentrations

Most studies show a gradual 2- to 4-fold increase in basal oxytocin levels during pregnancy.[8] The oxytocin-producing neurons in the SON and PVN have estrogen receptors, such as estrogen-beta receptors, through which estrogen activation promotes the synthesis and release of oxytocin.[15–17] As circulating estrogen levels rise substantially during pregnancy, the increased concentrations of oxytocin may at least, in part, be secondary to the increased levels of estrogen. Some studies indicate that elevated oxytocin levels during pregnancy, in addition to the nonapeptide oxytocin, involve the release of an elongated oxytocin molecule.[50]

Toward term, oxytocin pulses appear in the circulation, and uterine contractions start to appear.[8] Data obtained from rodents suggest that a central opioidergic mechanism, possibly mediated via mu-opioid receptors, actively inhibits peak levels of oxytocin during pregnancy. Allopregnanolone, a neuroactive metabolite of progesterone present in increasing amounts in the brain during pregnancy, mediates this inhibitory effect on the oxytocin neurons by stimulating the inhibitory opioidergic mechanism via gamma-aminobutyric acid A receptors. As demonstrated in animal experiments, this opioidergic inhibition is withdrawn as the production of progesterone decreases toward the end of pregnancy, allowing peak levels of oxytocin to occur.[72–76] This endogenous inhibitory mechanism is intended to reduce the risk of premature labor. In addition, the limited amounts of oxytocin in the hypothalamus and posterior pituitary are stored until labor starts, thus enabling the massive release of oxytocin that is necessary during labor and delivery.[15]

Whether this opioidergic mechanism is present in humans or whether another mechanism mediates the inhibition of oxytocin neurons during pregnancy is not known. Moreover, progesterone levels do not decline in humans and nonhuman primates toward the end of pregnancy. In vivo studies of oxytocin neurons during pregnancy in women may be performed in the future using modern molecular imaging techniques.

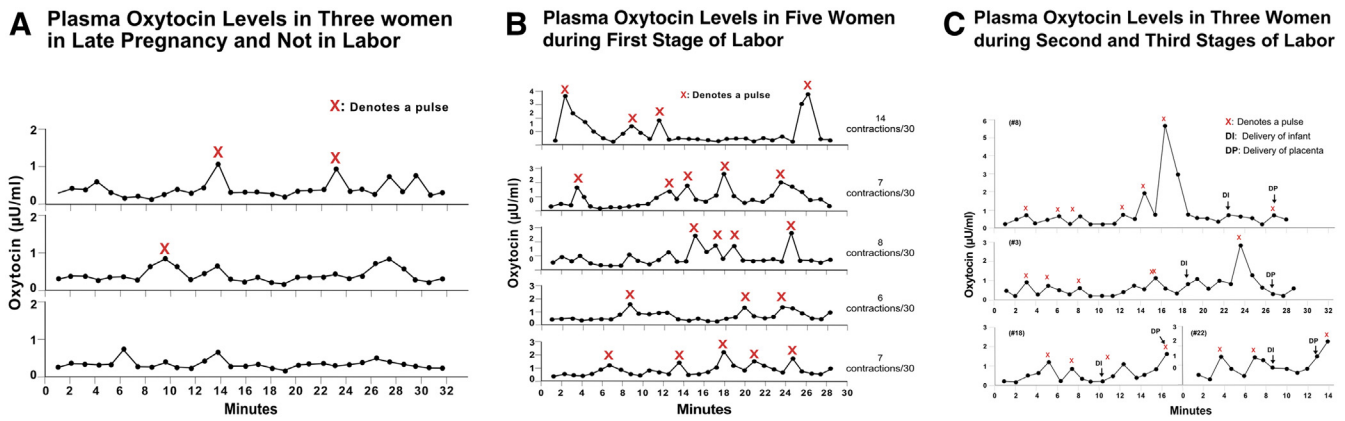
The number of oxytocin receptors in the uterus increases substantially from the beginning of pregnancy to reach maximal levels at term. A 100-fold increase in the number of oxytocin receptors has been found in the human myometrium concerning the onset of labor.[60] This increase in receptor density is likely to a large extent caused by the gradual increase of the availability of estrogens in the circulation during pregnancy, which leads to an activation of the oxytocin receptor gene.[8,15,60–62] The increased amount of oxytocin receptors and function will allow small increases in circulating oxytocin levels to induce contractions of the myometrium at term, which further reduces the need for oxytocin during labor, which is important given the limited amounts of available oxytocin.

Labor and delivery

Plasma concentrations of oxytocin during labor and the postpartum period

Labor is associated with short-lasting pulses of oxytocin.[8,77–88] which occur more frequently as labor progresses to reach a maximal frequency of 3 pulses per 10 minutes at the end of the second stage of labor.[77] Figure 5 demonstrates the presence of occasional oxytocin pulses at term pregnancy (Figure 5, A), an increasing frequency of pulses during the first (Figure 5, B) and second stages of labor, and a few pulses during the

FIGURE 5
Plasma oxytocin levels at term and during labor



The figure shows the pattern of peak levels of oxytocin in plasma at term pregnancy (**A**), first stage of labor (**B**), and second and third stages of labor (**C**). Samples were collected at 1-minute intervals from an indwelling catheter in the right arm. Data plots were chosen to show the highest and lowest pulse frequencies and amplitudes in each group. Each identified pulse is denoted with a *cross*. The figures are reproduced with permission from Fuchs et al,[78] with the courtesy of Dr Roberto Romero, who is a coauthor of the article.

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third stage of labor (Figure 5, C). The figures are based on data from Fuchs et al.[78]

In addition, the amount of oxytocin released with each pulse increases over time as labor progresses.[78] As a consequence of the more frequent pulses, average plasma oxytocin concentrations double during labor compared with oxytocin levels at term.[77] A very pronounced peak level of oxytocin often occurs concerning the delivery of the fetus.[81–85] Some articles show decreased oxytocin levels after delivery, indicating a fall from higher levels during labor. Several studies show that there is no direct correlation in time between uterine contractions and peak levels of oxytocin during spontaneous labor.[8,79,82,85,86,88]

Electrophysiological aspects of the oxytocin pulses

The oxytocin released into the circulation derives from oxytocinergic neurons that project to the posterior pituitary. The oxytocin-producing cells in the SON and PVN have been shown to get closer to each other because of retraction of the surrounding glial cells in response to the strong stimulation of the oxytocin-producing cells, such as during birth and breastfeeding.[89,90] As a consequence, the electrical action potential of the individual magnocellular oxytocin-secreting cells starts to synchronize. When all the neurons burst in synchrony, an oxytocin pulse is released into the circulation.[91,92] Examples of short-lasting pulses of oxytocin in response to nipple stimulation in women close to term are illustrated in Figure 6. To demonstrate peak levels of oxytocin, 5 blood samples were collected at 15-second intervals in association with 5 uterine contractions. The peak shaped patterns of oxytocin among individuals showed different appearances, whereas the oxytocin pattern tended to be more similar concerning the contractions in the same individual. Furthermore, in some individuals, peak levels of oxytocin were only observed in 1 of 5 samples collected at 15-second intervals, illustrating how difficult it might be to record oxytocin pulses.[93]

Oxytocin-mediated stimulation of prostaglandin synthesis and release in labor

Prostaglandins play an important role in labor as they affect cervical ripening and myometrial contractility. As described previously, oxytocin promotes the production of prostaglandins[60,61,78,94–98]; it increases the production of prostaglandin F2-alpha, prostaglandin E2, and leukotrienes in the uterine decidua and prostaglandin E2 in the amnion.[13,14] The prostaglandins produced in the decidua induce local inflammation, which promotes the ripening of the cervix and stimulates the propagation of the myometrial contractions. Moreover, the prostaglandins in the membranes change the texture of the membranes, thereby making them more fragile and able to rupture in labor.[85,94–100]

The stimulation of prostaglandin release by oxytocin is mediated by circulating oxytocin[101] and by oxytocin locally produced in the decidua, amnion, and chorion.[11,12] The oxytocin released within these areas activates specific types of oxytocin receptors, within the same tissues, which are linked to the synthesis and release of prostaglandins, via a local, paracrine mechanism. The expression of both the tissue-specific oxytocin release and oxytocin receptors is promoted by estrogen.[11,12,77,85,94–100] The oxytocin released within the decidua and the chorioamniotic membranes is degraded by a local supply of oxytocinases, thereby further restraining the effect of the

locally released oxytocin to neighboring tissues.[102,103] These local, oxytocin-linked, prostaglandin-mediated inflammatory responses run counter to the effects of circulating oxytocin, which is linked to a powerful reduction of inflammatory reactions.[42]

Oxytocin and the third stage of labor

A large peak level of oxytocin often occurs during, or just after birth, perhaps as a result of the activation of the Ferguson reflex.[81−85] Thereafter, smaller peak levels of oxytocin are observed during a 30- to 60-minute period after birth, often coinciding with the delivery of the placenta.[104−106] In addition, oxytocin released during the third stage of labor reduces postpartum bleeding.

Role of the autonomic nervous system

The role of the autonomic nervous system during labor was recognized in older studies but has not been a subject of recent research. The results of these previous findings are often not included in newer research.[97]

Based on animal experiments, activation of the parasympathetic, cholinergic nerves innervating the uterus gives rise to uterine contractions and increased uterine blood flow. Moreover, activation of sympathetic nerves results in uterine contractions but decreases circulation.[107] Labor can be induced by electrical stimulation of paracervical tissues in pregnant guinea pigs, and the uterine sensitivity to the contractile effects of oxytocin increases following this treatment.[108,109] Furthermore, low-intensity stimulation of the hypogastric nerve (1−6 Hz and 1 mA), which did not induce any uterine contractions per se, induced uterine contractions during a simultaneous oxytocin infusion of subthreshold doses of synthetic oxytocin.[110,111] These results indicate that myometrial sensitivity to the contractile effects of oxytocin can be enhanced by a concomitant activation of the autonomic nervous system. Although the authors did not discuss it at the time, the facilitating effect induced by autonomic nervous activity on the ability of oxytocin to induce uterine contraction might be linked to an increased function of the myometrial oxytocin receptors.

Whether the activity of the autonomic nervous system plays a role in human labor and delivery is not known. The autonomic innervation of the uterus, both the sympathetic and parasympathetic branches, undergoes degenerative changes during pregnancy, as demonstrated both in animal studies and in women.[112] However, such degenerative changes do not occur in the more densely innervated cervix of the uterus, where the innervation remains intact. Therefore, nervous activity may still play an important role in controlling the function of the cervix and the rest of the uterus concerning labor.[113]

Knockout mice lacking the oxytocin gene were found to go into labor, suggesting that oxytocin may not be necessary for labor.[114] However, other studies showed that oxytocin antagonists and exposure to stress, which lower oxytocin levels, inhibited the progress of labor, indicating that oxytocin does contribute significantly to the progress of labor and delivery. In particular, oxytocin seemed to be important for the timing and onset of labor.[115,116] The data can be interpreted as if the oxytocin receptor may be even more essential for birth than oxytocin itself.[99]

The redundant mechanism by which labor is promoted in the absence of oxytocin might hypothetically involve the autonomic nervous system, particularly the parasympathetic branch.[107] From this point of view, it is interesting that mice that lack the oxytocin gene completely fail to eject milk in response to suckling and the offspring die. The absence of a redundant mechanism in the case of milk ejection may be due to the fact that the mammary glands lack parasympathetic innervation.[10]

Modulation of oxytocin release during labor

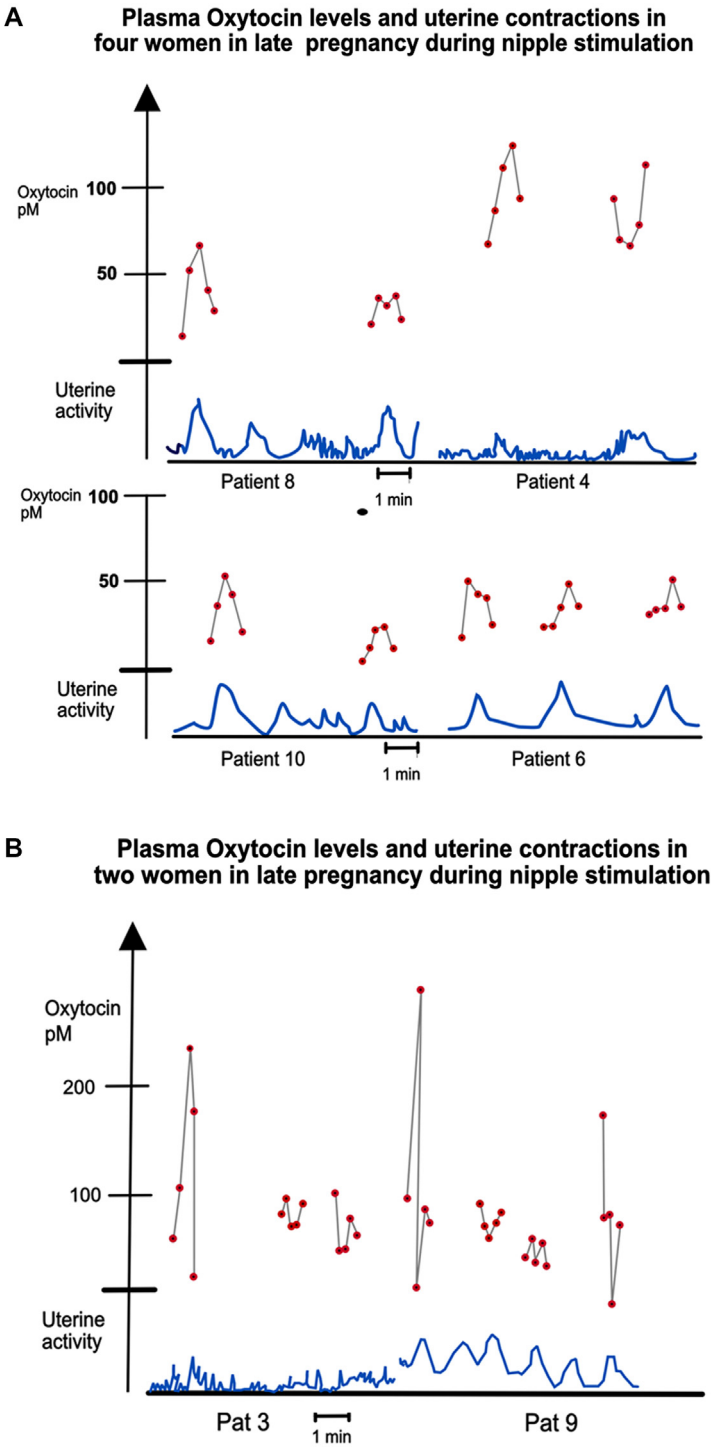
Reinforcement of oxytocin release

The frequency and size of peak levels of oxytocin in the circulation increase during the first and second stages of labor. The increase of oxytocin release during labor may, in part, be linked to repeated activation of the Ferguson reflex, which is mediated by sensory parasympathetic nerves that connect the uterus and the brain (Figure 7).[117,118] When the head of the fetus presses against the cervix and vaginal wall, mechanoreceptors are activated that stimulate the activity of afferent parasympathetic nerves, which terminate in the nucleus tractus solitarius (NTS). Noradrenergic fibers from the NTS project directly to, and activate, the oxytocin-producing neurons within the SON and PVN.[15,34,119] As the uterine contractions become more powerful, the pressure exerted by the fetal head on the cervix and the vaginal wall becomes stronger, which will lead to a more intense activation of the parasympathetic sensory nerves, and consequently, more oxytocin is released into the circulation from the SON and PVN. In this way, oxytocin concentrations in circulation increase over time. The mega-peak levels of oxytocin often described during labor and delivery birth might be due to a particularly strong activation of the Ferguson reflex during the delivery of the fetus.[81−85]

In animals, such as sheeps, a substantial rise of oxytocin levels occurs in the cerebrospinal fluid (CSF) during labor and delivery. The release of oxytocin into the CSF during labor and delivery is abolished if peridural analgesia is applied during labor and delivery, and it is enhanced by mechanical stimulation of the cervix. Overall, these findings suggest that the Ferguson reflex plays an important regulatory role in the release of oxytocin into the CSF during labor and delivery.[120]

The oxytocin released into the brain derives from the parvocellular neurons from the PVN and from axon collaterals of the magnocellular neurons of the SON and PVN.[28−32] In addition, a release of oxytocin from dendrites and cell bodies of the magnocellular neurons may contribute to the rise of oxytocin concentrations (Figure 2).[27] The oxytocin of dendritic origin diffuses into adjacent areas of the brain to activate oxytocin receptors and induce oxytocin effects. Interestingly, the dendrites of the oxytocin neurons are provided with oxytocin receptors, which, when

FIGURE 6
Plasma oxytocin levels in response to nipple stimulation



The figure shows pulses of oxytocin in plasma and uterine contractions in response to nipple stimulation in 6 women in late pregnancy (38—39 weeks of gestation) not in labor. Of note, 5 samples were collected at 15-second intervals from an indwelling catheter in the right arm during individual contractions. Plasma levels of oxytocin were measured with radioimmunoassay. Note that the peak levels of oxytocin correspond in time with uterine contractions, that their appearance varies between different women, and that the peak level sometimes can be observed in only 1 sample. In **(A)** data from 4 women are shown and in **(B)**, 2 women with particularly high oxytocin levels are shown. The figures are redrawn based on data published by Christensson et al.[93]

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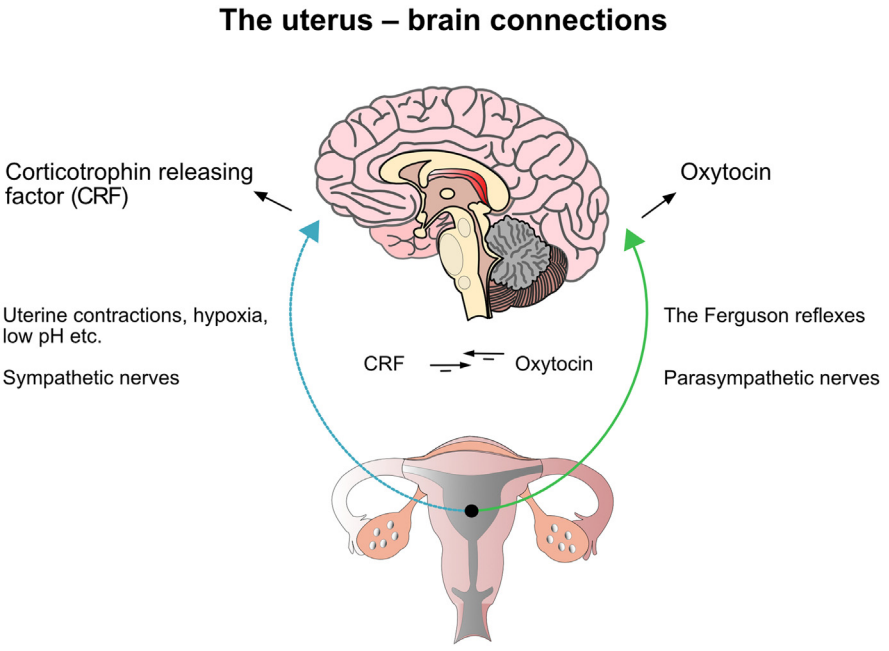
activated by oxytocin, further stimulate the release of dendritic oxytocin. In this way, a central feedforward mechanism for the dendritic release of oxytocin is established.[121,122]

The oxytocin released into the brain of sheep during labor and delivery is associated with the onset of maternal behavior and bonding with the newborn. The administration of peridural analgesia, which blocks the intracerebral release of oxytocin, and the administration of oxytocin antagonists, which block the effects of oxytocin, abolish these behaviors.[120] Maternal sensation of pain and the levels of fear and stress are reduced by oxytocin released in the brain. In addition, oxytocin may, via effects in the central amygdala, reduce the long-term memory of pain and fear of labor and delivery.[123,124]

Whether similar effects are present in women during labor and delivery remains to be established, but the levels of oxytocin increase in CSF of human mothers during labor. However, an oxytocin mediated stimulation of maternal interaction and bonding with the newborns, a potent reduction of fear, pain and stress as well as an activation of dopaminergic neurons have been established in mothers during skin-to-skin contact after birth as well as in connection with breastfeeding.[8–10,71,125–129]

Oxytocin release may be affected negatively during labor. Activation of sympathetic afferent nerves and pain-mediating fibers increases sympathetic nervous activity and decreases oxytocin release (Figure 7).[130]

FIGURE 7
Nervous connections between the uterus and the brain



The Ferguson reflexes or parasympathetic sensory nerves are activated by the pressure exerted by the head of the fetus on the cervix and lead to an increase of oxytocin levels in the circulation and the brain. Sympathetic afferents from the myometrium are activated by myometrial contractions which decrease the release of oxytocin.

CRH, corticotropin-releasing factor.

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Intravenous administration of synthetic oxytocin for induction and augmentation of labor

Intravenous administration of oxytocin is often given to induce or augment labor. The percentage of nulliparous women that receive oxytocin infusion during labor in Sweden is approximately 70%, compared with 30% in multiparous women. The use of oxytocin during labor is increasing. In women who receive synthetic oxytocin infusion because of delayed progress of labor, the administration of oxytocin may shorten the duration of labor until birth by approximately 2 hours, but the number of cesarean deliveries is not changed.[131,132]

The amounts of oxytocin administered during labor and delivery are most often expressed in international units or milli-international units of oxytocin. When converted to weight units, 1 IU of oxytocin corresponds to 1.67 μg of oxytocin and 1 mIU corresponds to 1.67 ng of oxytocin. Oxytocin concentrations (eg, in blood and plasma) are expressed either as microunit per milliliter or picogram per milliliter. The concentration of 1 μU/mL of oxytocin corresponds to 1.67 pg/mL of oxytocin.

Actions of exogenous oxytocin on myometrial contractions

According to Fuchs et al[78], the lowest effective amount of oxytocin, given as an intravenous bolus dose for induction of myometrial contractions, was shown to be between 4 and 8 mIU. These amounts of oxytocin administered as an intravenous bolus gave rise to elevations of plasma concentrations of oxytocin, which were comparable to the size of peak levels of oxytocin recorded during spontaneous labor. There was no immediate temporal relationship between the peak levels of oxytocin and the contractions induced, but there was a relationship between the amplitude of the peak level and the number of uterine contractions induced by bolus administrations.[78]

Oxytocin infusion rates

Infusions of synthetic oxytocin often start at low rates, such as 1 to 3 mIU/minute. The infusion rate is increased at 15- to 40-minute intervals usually by a stepwise increase of a set amount of oxytocin or by doubling the dose until contractions are initiated. The maximal rate of infusion of synthetic oxytocin

rarely exceeds 32 mIU/minute in many clinical settings.[133] In a recent survey performed in 12 European countries, a substantial variation regarding dose regimens was observed. Starting rates varied from 1 to 15 mIU/min (0.06−0.90 IU/h), and maximal infusion rates varied from 15 to 60 mIU/min (0.90−3.60 IU/h). In addition, the interval between changes in the infusion rate varied. The predicted total amount of synthetic oxytocin infused during 8 hours varied between 2.38 and 27.00 IU; however, in most countries studied, the calculated 8-hour dose was 7 to 8 IU.[133] These data demonstrate that the rate of oxytocin infusion and the total amount of synthetic oxytocin administered during labor vary substantially between countries in Europe. More synthetic oxytocin might be given in other countries (eg, in the United States).

The sensitivity to oxytocin varies among pregnant women. In 1 study, adequate myometrial contractions were obtained by infusion rates of synthetic oxytocin varying between 0.9 and 5 mIU/minute. The reason behind this variation is not known, but the different sensitivity of the oxytocin receptors may include factors, such as different exposures or effects of increased estrogen levels during pregnancy, different body mass indices, and age of the woman.[61]

Some studies, but not all, show that if synthetic oxytocin is administered in pulses and not as a continuous infusion, similar results regarding the duration of labor concerning induction or augmentation of labor are obtained, but less oxytocin may be needed.[134−137] This may indicate that the physiological administration of oxytocin (in pulses) is more efficient than the stable rate of administration in response to infusion of oxytocin.[138] Whether peak levels of oxytocin still occur during infusions of synthetic oxytocin is not known; however, 1 study suggests that pulsatile oxytocin is blunted after infusion of oxytocin.[139]

Plasma oxytocin concentrations in response to infusion with synthetic oxytocin

Plasma oxytocin concentrations have been measured after infusion with synthetic oxytocin during labor.[77,140−146] Dose-response curves have been performed in both connection with induction[75,142] and augmentation of labor,[140,141] and similar-sized dose-dependent increments of oxytocin concentrations were observed. As measured by RIA, the plasma oxytocin concentration rose by 1 to 2 pg/mL in response to an increase of the infusion rate by 1 mIU/min.[140,142] In all of these dose-response studies, oxytocin levels were measured using RIA. No dose-response study has been performed in which oxytocin levels were measured using ELISA. Of note, 1 study that measured both the average rise of oxytocin concentrations occurring during spontaneous, physiological labor and the increase of oxytocin concentrations in response to infusions of synthetic oxytocin found that infusion rates up to 10 mIU/min (0.6 IU/h) raised oxytocin concentrations to levels normally observed during the second stage of labor (from basal concentrations of 20 to 40 pg/mL). However, at higher infusion rates, a further 2- to 3-fold increase of oxytocin concentrations above those recorded at an infusion rate of 10 mIU/minute was observed. This means that plasma oxytocin concentrations rarely exceed 100 to 150 pg/mL during infusion of synthetic oxytocin during labor if recommended dose regimens are used.[77] Steady-state oxytocin levels were obtained within 40 minutes of infusion. As the half-life of oxytocin in plasma is relatively short (3−6 minutes),[54,55] basal oxytocin concentrations are soon reached after infusions of synthetic oxytocin have been stopped. Moreover, it should be pointed out that individual oxytocin pulses during labor can reach quite substantial concentrations for a short period (Figure 4).

Hyperstimulation

The amount of oxytocin administered is crucial, as too high levels of oxytocin may induce hyperstimulation of the myometrium, including excessive frequency of contractions. This may harm the fetus as the placental and fetal blood flow may become compromised with consequent fetal hypoxia.[147−150] Discontinuation of the oxytocin infusion is the standard approach to minimize the negative consequences of hyperstimulation concerning infusions of oxytocin.[150]

Recent studies show that if oxytocin infusions are performed within the recommended dose levels, they are safe. A recent multicenter, randomized study evaluated the effect of discontinuing oxytocin infusion when reaching the active phase of labor. This intervention, which is associated with a decrease in the amount of administered oxytocin, did not improve neonatal morbidity or increase the rate of other neonatal or maternal negative outcomes.[151] In another study, the risk of adverse outcomes in response to infusion rates higher than 20 mIU/minute were compared with those induced by infusion of oxytocin at lower rates. In this double-blind randomized controlled trial, no significant difference in maternal or perinatal adverse outcomes was found when the effects of the 2 dose levels were compared.[152]

Whether circulating oxytocin from the maternal circulation passes the placenta and maternal blood-brain barrier has become a matter of debate. It has been suggested that maternal circulating oxytocin levels become extremely high in response to infusions of synthetic oxytocin and that oxytocin under these circumstances would pass through the placenta and the maternal blood-brain barrier and negatively affect the fetus and the maternal brain.[153,154] However, there is little scientific support for a transfer of oxytocin over the placenta if oxytocin is infused during labor according to recommendations. As stated above quite small amounts (5−10 IU) of synthetic oxytocin are infused, often for a period of several hours during labor, and therefore maternal plasma oxytocin concentration are only moderately elevated. In clinical studies in which both maternal and oxytocin fetal oxytocin concentrations were measured after birth, there is no evidence of any passage of oxytocin from the mother to the fetus.[155] Fetal plasma oxytocin concentrations are higher than maternal oxytocin concentrations in terms of

vaginal birth, suggesting a fetal production of oxytocin.[156] Furthermore, oxytocin, being a polar peptide, does not easily pass biological membranes, and only 0.1% to 1.0% of a given dose of oxytocin passes over the blood-brain barrier.[59] Overall, these data indicate that infusions of synthetic oxytocin within the recommended dose range do not influence the fetus or the mother by passing through the placenta or blood-brain barrier during labor. However, the dose of oxytocin administered is crucial. If higher amounts of oxytocin are given, oxytocin may pass the placenta and maternal blood-brain barrier.

In addition, some animal data suggest the presence of a local transport system for oxytocin from blood to areas in the brain, such as the amygdala, the receptor for advanced glycation end products (RAGE) system. In animal experiments, the RAGE system has been shown to promote maternal interaction with her pups, possibly because of the transfer of oxytocin from the circulation to the brain. Whether a similar effect occurs during physiological and induced labor in women is not yet known.[157]

Postpartum administration of oxytocin

An intramuscular or intravenous administration of 5 to 10 IU of oxytocin is often given routinely at the time of the expulsion of the posterior arm of the fetus to induce uterine contractility, to promote placental separation, and to decrease the risk of PPH.[158–160] The amount of synthetic oxytocin contained in the bolus dose given after delivery is similar to the average amount of synthetic oxytocin administered during labor, and consequently, maternal oxytocin concentrations are very high (700 pg/mL) immediately after the administration of the postpartum bolus administration. Thereafter, oxytocin levels decrease rapidly and reach basal levels within 1 hour.[161] Moreover, high oxytocin levels were observed after intravenous bolus administration of 10 IU of synthetic oxytocin to women experiencing menopause (oxytocin levels of >2000 pg/mL).[55] Intramuscular and subcutaneous administration of oxytocin after delivery leads to delayed absorption of oxytocin and consequently to lower oxytocin levels, compared with intravenous administration.[161]

Cardiovascular events have been reported after bolus administration of oxytocin. For example, a fall in blood pressure, transient tachycardia, and chest pain were reported after intravenous administration of 10 IU of synthetic oxytocin to women who have received epidural analgesia during cesarean delivery. In addition, the ST segment of the electrocardiogram was depressed, and troponin levels were increased in some of these women, indicating a possible occurrence of ischemic tissue damage in the heart. The cardiovascular effects disappeared or were reduced when the bolus dose of oxytocin was reduced to ≤5 IU or the route of administration of oxytocin was changed from intravenous to intramuscular.[162–165] The cardiac pain may be caused by a cardiac vasoconstrictor effect as a consequence of the hypotension and tachycardia caused by the administration of oxytocin. Moreover, the contractile effects on cardiac blood vessels may be caused by a direct effect of oxytocin on cardiac oxytocin receptors, or possibly on vasopressin receptors, as oxytocin in very high levels may bind to and cross-react with vasopressin receptors.[15]

Down-regulation of oxytocin receptors

The administration of oxytocin for labor induction or augmentation has been suggested to increase the risk of PPH, and some patients who receive oxytocin develop myometrial hypodynamia. This effect has been attributed to the desensitization of the oxytocin receptor in response to prolonged exposure to oxytocin.[166–169]

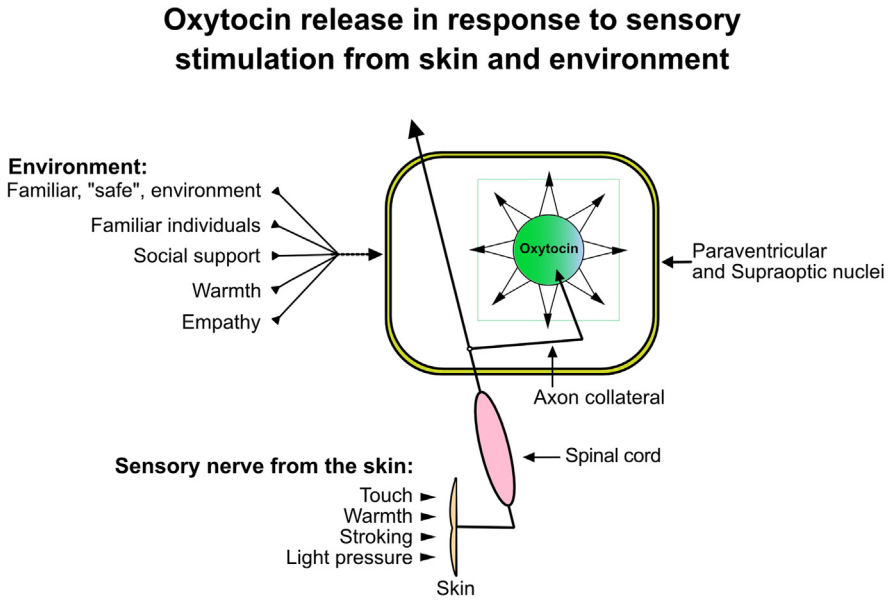
The levels of oxytocin receptor mRNA and protein synthesis have been shown to be reduced in these situations showing that there is a down-regulation of the production of the oxytocin receptor. It has been suggested that this reduction of the function of oxytocin receptors is due to a direct inhibitory effect by circulating oxytocin concentrations on the oxytocin receptors, caused by the high levels of oxytocin induced by infusions of synthetic oxytocin. In vitro experiments support this assumption. When oxytocin receptors are exposed to nanomolar or micromolar concentrations of oxytocin for 5 to 10 hours, a decrease in oxytocin receptor mRNA has been demonstrated.[64–67] However, the very high concentrations of oxytocin and the long exposure time needed in these experiments for down-regulation of oxytocin receptor mRNA suggest that the results do not represent physiological conditions, as plasma oxytocin concentrations in response to infusions of synthetic oxytocin are within the picomolar range. The down-regulation or desensitization of the oxytocin receptors may be due to another mechanism, for example, related to a physiological feedback inhibition of the function of the oxytocin receptors.

Social support and activation of the oxytocinergic system

Social support is a well-known concept within the field of psychology. The presence of a supportive person decreases stress levels, including cortisol levels and inflammatory markers, and perceived anxiety in individuals of different age and sex groups, suggesting a down-regulation of the stress system.[170]

A similar calming effect may be induced by the presence of a supportive person during labor and delivery. The presence of a supportive person during labor shortens its duration, decreases the rate of cesarean delivery, and reduces the use of medical interventions, such as epidural analgesia and infusions of synthetic oxytocin.[1,171–173] In addition, studies show that mothers participating in midwife-led continuity models of care during pregnancy were more likely to have a spontaneous vaginal delivery and less likely to have regional analgesia, instrumental vaginal delivery, preterm birth (<37 weeks of gestation), and fetal loss.[174] It is important to mention that not all studies performed show a positive effect of social support on birth, and more clinical studies and evidence regarding the effect of social support are needed before it could be introduced as a clinical practice.

FIGURE 8
Oxytocin release in response to activation of cutaneous sensory nerves



The cutaneous sensory nerves respond to touch, stroking, light pressure, and warmth and may correspond to unmyelinated C-tactile fibers and to thicker myelinated nerve fibers. In addition, analogous mental triggers mediating information about safety, familiarity, support, warmth, and empathy may hypothetically trigger oxytocin release. This model demonstrates how the release of oxytocin from parvocellular neurons in the SON and PVN during labor can be reinforced by activation of cutaneous sensory nerves.

PVN, paraventricular nucleus; *SON*, supraoptic nucleus.

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Social support may hypothetically act by modulation of oxytocin release concerning labor and delivery.[175] Of note, 1 study investigated the pulsatile oxytocin pattern during labor but found no effect of social support on oxytocin levels.[176] However, the effects of social support are not likely to act via a release of oxytocin from the magnocellular oxytocin neurons in the SON and PVN into the circulation but rather by effects of oxytocin released from neurons within the brain.

In animals, environmental cues that signal calmness and safety have been shown to activate specific nerve fibers in the cortex, which, via the amygdala-hippocampal pathway, innervate the parvocellular oxytocinergic neurons of the PVN.[17,26] Hypothetically, the presence of a person, who is experienced as friendly, warm, empathic, and supportive, may actively stimulate such oxytocin neurons in the brain.

In addition, touch or sensory stimulation of the skin may contribute to the positive effects exerted by a supportive person on the progress or experience of labor. Several studies show that oxytocin can be released and that oxytocin mRNA in the PVN can be increased in response to touch via stimulation of cutaneous sensory nerves (Figure 8). Such stimulation does not induce a pulsatile release of oxytocin but may or may not be associated with increased levels of circulating oxytocin[2,34,119,177] Recent studies performed by Grinevich and colleagues show that parvocellular oxytocinergic neurons in the brain are activated in response to touch and social stimuli.[178,179] Moreover, activation of the oxytocin neurons in response to touch may reduce pain and stress levels.[123,124]

Epigenetic and genetic influence on the oxytocinergic system

Animal experiments show that long-term behavioral and physiological effects can be induced in the perinatal period, by how mothers handle their infants.[180] Some mothers provide their neonates with more tactile interaction than others do. Neonates receiving extra tactile stimulation or are given extra oxytocin become more social and less prone to stress reactions as adults, compared with those who do not receive these treatments. These changes possibly involve epigenetic change with differences in the levels of methylation of the oxytocin and cortisol receptor genes.[23,181–184]

Some data implicate that the amount of positive mother-infant interaction in early life is associated with decreased DNA methylation of the oxytocin receptor gene in the neonate, whereas other authors suggest that these data should be regarded with caution.[185–187] To date, there is no data that demonstrates epigenetic changes of the oxytocin gene or oxytocin receptor gene in connection with labor or delivery in humans, but there is great interest in this research topic.[68,188]

Single-nucleotide polymorphisms

Data are emerging that show that single-nucleotide polymorphisms (SNPs) in the oxytocin receptor may influence different aspects of labor. Some of these receptor variants are linked to variations in the effect of oxytocin on myometrial contractility, to the dose requirements regarding infusion of oxytocin, to susceptibility to preterm birth, and to the risk of PPH. Moreover, the effects of SNPs may involve the function of intracellular signaling pathways activated by the oxytocin receptor.[189–193] This is a rapidly growing field of research, and more findings are to be expected soon.

Conclusions

Oxytocin is a system involving hormonal, neurosignaling, and paracrine effects. It has multiple important effects

Glossary

Allopregnanolone: A neuroactive metabolite of progesterone
Amino-terminal: The end of a peptide containing an amino group
Aprotinin (Trasylol): A substance that inhibits the activity of degrading enzymes
Beta-arrestin: A molecule that helps move oxytocin receptors from the surface into the cells
Calmodulin: A substance involved in the intracellular signaling after oxytocin has bound to its receptor
Carboxy-terminal (C-terminal): The end of a peptide containing a carboxyl group
Enzyme-linked immunosorbent assay (ELISA): An immunologic method used for the determination of oxytocin levels
G-protein—coupled receptor: A group of receptors that transfer information from the cell membrane into the cell via G proteins
Hydrophilic: A substance that can be dissolved in water
Isotocin: An oxytocinlike substance in fish
Magnocellular neurons: Large oxytocin producing neurons in the SON and PVN
Mesotocin: An oxytocinlike substance in birds
Methylation: Methylation of DNA in the promoter region of genes reduces the synthesis of proteins
Mitogen-activated protein kinase (MAPK): A substance involved in the intracellular signaling leading to production of prostaglandins after oxytocin has bound to its receptor
Myosin light-chain kinase: A substance involved in the intracellular signaling after oxytocin has bound to its receptor
Neurophysin: A peptide that is synthesized together with oxytocin but cleft off before release into the circulation
Nucleus solitarius (NTS): Important integrative center for autonomic nervous function in the brain stem
Oxytocinase: An enzyme that degrades oxytocin
Paraventricular nucleus (PVN): One of the major sites of oxytocin neurons in the hypothalamus
Parvocellular neurons: Small oxytocin-producing neurons in the PVN
Phospholipase-C: A substance involved in the intracellular signaling after oxytocin has bound to its receptor
Placental leucin-amino-peptidase: An oxytocin degrading enzyme, which is produced in the placenta
Radioimmunoassay (RIA): A method used for the determination of oxytocin levels, involving radioactivity
Receptor for advanced glycation end products (RAGE): A receptor that may actively transport oxytocin over the blood-brain barrier
Supraoptic nucleus (SON): One of the major sites of oxytocin neurons in the hypothalamus

during labor, and several oxytocin-linked mechanisms cooperate to promote the birth of the neonate. Oxytocin stimulates uterine contractions by activating oxytocin receptors in the myometrium. Moreover, it stimulates the secretion of prostaglandins via a local, paracrine effect in the decidua and amnion. In the future, oxytocin may be shown to induce effects in the maternal brain to facilitate labor and delivery; to decrease levels of pain, fear, and stress; and to adapt the mother for motherhood.

Infusions of synthetic oxytocin may be administered to shorten labor or as a bolus after delivery to decrease the risk of PPH. The plasma concentrations of oxytocin are only moderately elevated in response to infusions of synthetic oxytocin and are not likely to be associated with a passage through the placenta and maternal blood-brain barrier if given within recommended dose regimens. Social support may be used in the future to support mothers during labor and delivery. ■

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