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BEYOND LABOR: THE ROLE OF NATURAL AND SYNTHETIC OXYTOCIN IN THE TRANSITION TO MOTHERHOOD

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Abstract

Endogenous oxytocin is a key component in the transition to motherhood affecting molecular pathways that buffer stress reactivity, support positive mood, and regulate healthy mothering behaviors (including lactation). Synthetic oxytocin is widely used throughout labor and postpartum care in modern obstetrics. Yet research on the implications beyond labor of maternal exposure to perinatal synthetic oxytocin is rare. In this article, we review oxytocin-related biological pathways and behaviors associated with the transition to motherhood, and evidence supporting the need for further research on potential effects of intrapartum oxytocin beyond labor. We include a primer on oxytocin at the molecular level.

Keywords

oxytocin; birth; mothering; Pitocin; labor; stress; mood; postpartum depression; lactation; breastfeeding

Introduction

Consequences of routine childbirth interventions on human maternal behavior have been understudied. Synthetic oxytocin (Pitocin[®], Syntocinon[®]) stimulates uterine smooth muscle contractility and is widely used in the United States for labor induction, augmentation, and third stage management. While the judicious use of synthetic oxytocin has many benefits, the biological and behavioral effects of synthetic oxytocin beyond the immediate clinical uses remain largely unknown. According to the U.S. Centers for Disease Control and Prevention Vital Statistics report, induction has more than doubled from 1990 (10%) to 2010 (23%).¹ The best current estimate of the augmentation rate in the U.S. is 57%.² While endogenous oxytocin is well known for its role in labor and lactation, a large body of evidence documents numerous oxytocin-mediated molecular and endocrine pathways that buffer stress reactivity, support emotional and mental well-being, and promote pro-social and bonding behavior.^{3,4} These behaviors are critical for successful transition to motherhood. Given the predominance of synthetic oxytocin in clinical practice, research is needed on how synthetic oxytocin may impact the intrinsic regulation of endogenous oxytocin and subsequent oxytocin-related outcomes. In this review, we examine the hypothesis that exposure to synthetic oxytocin during childbirth may play a role in maternal stress reactivity, mood, and mothering behaviors (including lactation).

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OXYTOCIN ON THE MOLECULAR LEVEL

Profound changes occur in the oxytocin system during the perinatal period.^{5, 6} To prevent preterm birth, oxytocin neurons are kept quiescent during pregnancy through inhibitory mechanisms. The peptide oxytocin continues to accumulate in the posterior pituitary, and at term those inhibitory mechanisms are removed for labor to occur. Oxytocin also becomes more available at term through the reduction of enzymatic activity that metabolizes oxytocin in the brain. Based on animal studies, the expression of oxytocin receptors (OTR) increases throughout pregnancy in key areas of the brain that regulate mood, stress and attachment behavior. In humans, the availability of OTR in uterine muscle also increases dramatically at term, preparing for the surges of oxytocin about to be released during birth.

The neurologic origin of oxytocin

Oxytocin is a small neuropeptide consisting of nine amino acids.⁷ Throughout the human lifespan, specific neurons manufacture oxytocin; these cells are abundant in distinct areas of the mammalian hypothalamus called the paraventricular and supraoptic nuclei. Oxytocin from these cells is carried to and released from the posterior pituitary gland into the circulation, and from there is distributed throughout the body. Within the central nervous system, oxytocin reaches nearly all parts of the brainstem, midbrain, cortex, and spinal column. In addition to hypothalamic production, peripheral organs and tissues also may secrete oxytocin, but the pituitary is believed to be the predominant source of oxytocin in circulation.⁷

Oxytocin receptor: how oxytocin affects physiology in the brain and body

To affect target tissues, a receptor must be present and oxytocin presumably must bind to that receptor before it can exert cellular action. Oxytocin receptors (OTR) are found throughout the body, with particularly high concentrations in the limbic regions of the brain, spinal column, heart, intestines, immune tissue, uterus, and breast. The OTR belongs to a large family of receptors called G-protein coupled receptors, manufactured by the cell and inserted into the cell membrane where they are available for hormone-binding.⁷ G-protein Coupled Receptors loop in and out of the cell membrane seven times and are coupled to a G-protein located on the inside of the cell. Many varieties of G-proteins are known, each initiating a different cascade of events (second messengers) within the cell, which provides specificity to the hormone's action. The OTR is coupled to a G- α . This type of G-protein leads to a rise in intracellular calcium (Ca^{+}) and a muscle cell contraction, of particular importance to milk let-down and uterine contractions (see Figure 1).^{7, 8}

However, when the OTR is on a neuron, the response may be the subsequent release or inhibition of other hormonal neurotransmitters and modulators, such as serotonin, endogenous opioids and corticotrophin-releasing factor.³ These nervous system interactions are key to understanding how oxytocin released in the brain influences a variety of mental states and behavior. It may also help to explain how the nervous system is stimulated in response to a human or animal's environment (both external and internal) and subsequently leads to the release or inhibition of oxytocin. Additionally, oxytocin binds to other types of receptors, such as vasopressin receptors exerting agonist or antagonist effects, thus extending and diversifying the consequences of oxytocin's actions.

Oxytocin-mediated pathways beyond muscle contraction

Within all cells, not just neurons, three other important functions of the OTR lead to an array of possible cellular actions. 1) Through intracellular G-protein activation, phospholipase C causes an even greater amount of Ca^{+} release into the cell from internal stores. This Ca^{+} can serve as an independent signal for various functions within the cell, especially nerves. 2)

Another function is the creation of eicosanoids or prostaglandin that can directly increase pain, inflammation, and likely uterine contraction as well. 3) Thirdly, OTR activation may lead to a broad category of cellular events by activating a specific kinase, an enzyme that catalyzes the addition of a phosphate group on a specific target molecule or protein. In this instance, protein kinase C is activated and requires Ca⁺. The “downstream” effects of OTR activation will depend on what type of cell the receptor is located on. This kinase may initiate a specific action itself or cause another kinase to activate, and then another, creating a literal cascade of events.⁷ These events can ultimately lead to modifying gene transcription, regulation of the cell cycle, apoptosis and/or neurogenesis. The end result for each oxytocin-initiated pathway depends on the type of cell involved (uterine, brain, heart etc.) and the type of response initiated within that cell. OTR activation has the potential for inducing long-lasting biological alterations.

CHALLENGES IN STUDYING OXYTOCIN ON THE MOLECULAR LEVEL— BRAIN VERSUS BODY

In the intrapartum setting, the half-life of Pitocin[®] is believed to be only a few minutes,⁹ and intrapartum plasma levels correlate with Pitocin[®] dose and rate of administration,¹⁰ yet the dose delivered intravenously may or may not result in an effective uterine contraction pattern. Similarly, oxytocin levels in plasma cannot always be interpreted as being meaningful in a particular effect on brain activity. In order to understand how perinatal oxytocin exposure has the potential for lasting biologic consequence, it is helpful to understand some of the constraints that can limit research or the interpretation of research in this field. Many research studies examining endogenous oxytocin in animals and humans rely on blood measurement of the hormone in response to a treatment or intervention, e.g. a stressful event or a social interaction. There are several challenges in the interpretation of these measurements.

Firstly, central nervous system oxytocin is secreted continuously acting within the brain and spinal cord, but oxytocin is also released in pulses into the bloodstream through the posterior pituitary. Pulsatile release of oxytocin occurs when oxytocin neurons of the posterior pituitary depolarize, which are usually in response to specific stimuli (e.g., uterine stimuli or cues from an infant).^{11, 12} This activation of neurons pulses oxytocin into the blood stream. Data collected in rats suggest correlations between endogenous peripheral (blood stream) and central oxytocin levels, although the degree and significance of these correlations vary.¹³

In addition, there is controversy regarding whether peripherally administered oxytocin (i.e. Pitocin[®] given intravenously or intramuscularly) crosses the blood-brain barrier. Whether any oxytocin that does cross changes neuronal action significantly within the nervous system has yet to be determined.¹⁴ In theory, oxytocin cannot pharmacologically cross due to its relatively large size and hydrophilic nature, however, some animal studies do report low levels of oxytocin found in the brain following administration in blood¹⁵ Interestingly, some electrophysiology-based animal studies suggest that maternal oxytocin plays a neuroprotective role within the fetal brain during the birth process, which means it would have to cross both the placental barrier and fetal blood-brain barrier.¹⁶ The findings from these studies suggest that maternal oxytocin inhibits certain excitatory (GABA) fetal neurons from firing (depolarizing), thereby protecting them during periods of hypoxia (i.e. birth process). However, whether or not synthetic or endogenous oxytocin penetrates the maternal brain directly has yet to be proven. While oxytocin does leave the posterior pituitary and is released into circulation, this occurs following neuronal activation (action potential). Getting the peripherally circulating hormone into the brain would require either 1) an active transport mechanism to penetrate the tight junctions guarding the

microvasculature of the central nervous system (which has yet to be proven), or 2) it would require a more porous barrier to allow for diffusion.¹⁷ The blood-brain barrier (maternal or fetal) may become more porous in states of illness or stress.

Lastly, the brain may receive information about peripheral levels of oxytocin through feedback from peripheral nervous system. Peripheral nerves may communicate information about oxytocin levels to the brain, presumably via a feedback loop (e.g. cervical dilation, adrenal gland activity, touch/ nipple stimulation). There are also well-studied effects of intranasal administration of synthetic oxytocin on mood and social behavior, yet it remains unknown whether the intranasal route allows oxytocin to enter the brain directly or extraneuronally, or whether it stimulates feed forward effects on endogenous oxytocin via ascending or afferent neuropathways (i.e. the vagus or 10th cranial nerve), which are well known to have OTRs.¹⁴⁻¹⁸ Peripheral feedback effects of oxytocin, which may be relayed to the brain, are difficult to monitor, but further complicate the study of synthetic oxytocin. Whether the maternal brain will reliably respond to exogenous oxytocin by decreasing or increasing the synthesis or release of endogenous oxytocin is unknown. In the clinical setting, this type of feedback might be seen when Pitocin[®] is used to initiate an induction of labor but then can sometimes be shut off while the woman continues to labor without the drug. Likely, feedback from peripheral nerves messaging about cervical dilation to the brain is in action, which promotes the woman's endogenous oxytocin release, and this is more probable than the idea that Pitocin[®] penetrates the maternal brain directly.

However, given all these variables, altered maternal plasma levels persisting beyond the end of labor have been suggested in one study that evaluated postpartum oxytocin levels in response to breastfeeding two days after birth in women who had different intrapartum and postpartum exposures to synthetic oxytocin ($n=40$).¹⁹ Compared to all other study groups, women exposed to Pitocin[®] in labor combined with an epidural demonstrated significantly lower oxytocin levels during breastfeeding. Overall, the total quantity of synthetic oxytocin administered during parturition was negatively correlated to levels of oxytocin in plasma two days following birth. All of these women had vaginal births and newborns had normal Apgar scores. In these studies the mean duration of labor did not differ significantly between groups, nor did blood loss, or newborn weight. The women all initiated breastfeeding within minutes of birth and had the same average number of feeds in the days prior to the blood sampling. If replicable, this finding suggests that in some cases exposure to Pitocin[®] may have maternal consequences that last beyond the birth experience.

Altering the oxytocin receptor could change how oxytocin works

As reviewed above, the OTR must be present for oxytocin to exert its action. An important consideration for whether synthetic oxytocin may affect maternal physiology is the capacity of the OTR to become saturated. In response to saturation, sometimes a receptor is *internalized*, (i.e., removed from the cell-membrane where it is presumed to be unavailable and potentially degraded). In the presence of high levels of an agonist, receptor internalization may begin within minutes. The reverse process has been shown to take approximately four hours to resensitize after the agonist is removed.²⁰ However, work on sensitization has focused on myometrial cells, studied *in vitro*, and it is unknown if OTR on neurons will internalize and resensitize on the cell membrane *in vivo*. If neuronal OTRs undergo a comparable process, this could have implications for maternal behavior.

Another strategy against saturation is that receptors may be *internalized* and then *down-regulated*, through a pause in mRNA gene transcription for the receptor.²⁰ Research on induced labor in humans has focused on sampling the myometrium for expression of the OTR gene.²¹ One example is a study that compared women in spontaneous labor with those undergoing an induction of labor and 29 women who planned elective cesarean delivery.

Eighteen of the 33 women in the spontaneous group eventually received augmentation with synthetic oxytocin while 26 of 30 women of the induced group did as well. All laboring participants underwent cesarean delivery (indicated for failure to progress or fetal intolerance to labor) and the myometrium was sampled at that time. Oxytocin binding, as well as mRNA levels of the OTR, was significantly affected by use of synthetic oxytocin. Participants with oxytocin-induced labor had a 300-fold down-regulation of the OTR gene in uterine muscle, when compared to receptor availability in spontaneous labor.²¹ This study suggests that the OTR can down-regulate in the uterus during augmented or induced labor, and points to the need to study oxytocin binding in other areas of the body such as the maternal brain, breast, heart, intestine or immune system. Whether “active management” of third stage of labor also results in down-regulation of receptors has not been reported, but given the prevalence of this practice, it deserves consideration.

The duration of mRNA down-regulation in the OTR in response to synthetic oxytocin is not yet known. Considering the cellular mechanism for receptor regeneration would include mRNA transcription, translation, protein assembly/folding and transport to the cell membrane, this could take many more hours than simple internalization of the receptor, and full restoration of a functional OTR might require days. Also, after a given tissue is no longer exposed to a saturating agonist (labor), and if there is no stimuli for releasing endogenous oxytocin (e.g. touch, breastfeeding), the response to the perceived “need” of the system may be different between different types of birth and postpartum experiences.

The role of epigenetic regulation of the OTR—On a more long-term level, receptor regulation also can occur at the level of gene transcription for the receptor through epigenetic modulation. For example, methylation is one mechanism through which gene expression is down regulated. Attachment of a methyl group (CH₃) can occur on specific sites along the DNA sequence. A receptor gene that is more heavily methylated selectively “silences” the gene, preventing activation for transcription. Methylation of the OTR gene is one example of a mechanism that can down-regulate OTR gene expression, with effects that may be heritable. For example, if the OTR gene is silenced, less OTR will be available on the cell membrane. In turn, the OTR is less available to bind with oxytocin potentially resulting in diminished biological and behavioral outcomes.²⁰

There are sensitive periods during mammalian development in which the environment can shape DNA methylation.²² For instance, rodent models show that early maternal care can be linked to patterns of methylation in both maternal and offspring phenotypes with a transgenerational effect.²³ Emerging evidence supports the hypothesis that epigenetic modification of the OTR has a role in social cognition, stress reactivity, and social behavioral disorders.²⁴ For example, one study has examined the role of methylation of the OTR in autism-affected persons. Hypermethylation of the region of DNA controlling the OTR was seen in blood samples of affected individuals compared to controls (*n*=20 matched pairs). This effect also was demonstrated in postmortem brain sampling of 8 matched patient-controls, showing a correlation between brain and blood methylation in the OTR.²⁵ Pilot data in rodents suggest that normal birth with endogenous oxytocin, as well as exposure to intrapartum synthetic oxytocin, may produce epigenetic modulation of the OTR by increasing methylation of sites in the OTR gene of the maternal hypothalamus.²⁶

OXYTOCIN AND TRANSITION TO MOTHERHOOD

The experience of giving birth and becoming a mother, particularly for the first time, demands a high level of physical and social interaction. Being able to sensitively care for the needs of the infant through synchronous mother-infant interaction is vital to the continuation of the family and species. The postpartum period is also characterized by drastic hormonal

shifts, transition to motherhood, coping with new stressors, physical pain, lactation and attachment - all of which involve the endogenous oxytocin system. Furthermore, modern parenting can include financial strains, work obligations, social isolation or limited support, and socio-cultural constructs about “good” mothering. Within this context, a difficult transition to motherhood holds the potential to lead to dysregulated stress reactivity, mood disturbances, susceptibility to less sensitive mothering, asynchronous mother-infant interaction, and poor infant attachment.

Stress Reactivity

The maternal brain is a distinctive biological state, characterized by a host of biochemical mechanisms supporting the well-being and survival of both mother and infant.⁶ Significant adaptations occur in the maternal oxytocin system, including protection from the stress and demands of the perinatal period. The dramatic rise of oxytocin during physiologic birth may play a role in buffering the stress hormones released by fear and pain during labor according to animal studies and some human work.²⁷ This adaptive response is likely a protective mechanism during the perinatal period, a time of intense stress.

The relationship between oxytocin and the HPA (hypothalamic-pituitary-adrenal) axis in the body’s response to stressful stimuli has been investigated primarily using rodent models.³ These demonstrate that pregnant animals have reduced reactivity to stressors via lowered plasma levels of corticotrophin releasing factor, adrenocorticotropin releasing factor, and cortisol. There is inhibition of both oxytocin and HPA neurons during pregnancy mainly due to an inhibitory opioid mechanism from increased allopregnanolone (a metabolite of progesterone).⁶ During lactation, oxytocin pulses in the brain increase and the hormone is secreted into circulation. Meanwhile brain levels of oxytocin also increase and influence the neurons linked to the stress response system. Lactating females react less to stressors and display less anxiety-like behavior than non-lactating females. In response to stress oxytocin increases, possibly as a protective mechanism against continued stress. This can be seen when cortisol and adrenocorticotropin releasing factor decrease after administration of synthetic oxytocin. Conversely, when an oxytocin antagonist is given to rats, their levels of cortisol increase. However, in humans the relationships among oxytocin, HPA function, and stress reactivity are less well characterized. Measurements of salivary oxytocin in lactating women suggest that oxytocin may increase prior to feeding, when women are preparing to breastfeed.¹¹ There is also a decrease in circulating HPA hormones immediately after breastfeeding is initiated. Likely this is due to oxytocin within the brain exerting an effect on neurons that activate the HPA axis and corticotrophin releasing factor. Lactating women show increased vagal tone, decreased blood pressure and decreased heart rate when compared to non-lactating women, especially in response to a stressor.²⁸ As discussed earlier the vagus nerve detects elevated levels of oxytocin within the body and can feedback to the brain via afferent pathways. There is increasing evidence of a role for oxytocin in buffering stress reactivity, suggesting that oxytocin and the HPA systems are intricately linked.²⁷

Maternal Mood

As with stress reactivity, a well-regulated oxytocin system is anxiolytic and confers protection against negative mood. Several studies have shown that intranasal administration of synthetic oxytocin has an anxiolytic effect in psychiatric disorders.¹⁴ Whether intrapartum synthetic oxytocin confers the same protective function as endogenous oxytocin on maternal mental health is more difficult to determine, especially in light of the complexity of contemporary birth practices. Maternal depression in the postpartum period is estimated to affect up to 19% of women.²⁹ Women experiencing negative mood are less likely to show positive mothering behaviors, and are less sensitive to infant needs.³⁰ The

decreased quality of mother-infant interaction may lead to suboptimal infant attachment,³¹ placing infants at risk for poor development.³²

While there are well-known predictors of postpartum negative mood (e.g., poor social support, stressful/adverse life events, and history of depression/anxiety), subjective and objective birth variables (i.e., complications, mode of delivery, increased use of interventions, and maternal perception of the experience) also may be predictors of maternal outcome.^{33, 34} However, little is known of the biological underpinnings linking birth variables to postpartum mood, the specific effect of exposure to synthetic oxytocin has not been teased apart. Use of synthetic oxytocin is often associated with preexisting complications, but even in low-risk situations synthetic oxytocin can precipitate a cascade of interventions and subsequent birth complications.³⁵ Whether exposure to synthetic oxytocin during childbirth affects postpartum mood is unknown. However, based on our knowledge of the actions of oxytocin in other situations and in tissues outside of the central nervous system, we would anticipate that any effects of synthetic oxytocin would be dose-dependent and would show individual differences, influenced by context and the history of the mother.³⁶

Rodent models can elucidate molecular pathways of mood that have been evolutionarily conserved in mammals.³⁷ For instance, serotonin and dopamine are mediators of oxytocin's anxiolytic actions in both humans and rodents. When endogenous oxytocin is genetically or pharmacologically blocked, anxiety-like and depression-like behavior increases in oxytocin-deficient knockout mice compared to wild-type mice.³⁸ In responding to a stressor, rats bred for "high anxiety" exhibit a higher release of central oxytocin and greater anxiety-like and depression-like symptoms than rats bred for "low anxiety".³⁹ Oxytocin is one of the evolutionarily conserved molecular pathways of mood.

In humans, numerous studies have found that atypical peripheral oxytocin levels (very high or very low) may be associated with elevated symptoms of depression, anxiety, or post-traumatic stress.⁴⁰ In one perinatal example ($n=74$), low levels of oxytocin in late pregnancy were associated with elevated symptoms of depression at two weeks postpartum, controlling for prepartum symptoms, socio-demographics, and birth-outcomes.⁴¹ Individual context, adversities across the life cycle, history of trauma, genotype, and epigenetic processes are all factors that may program the oxytocin system altering (and possibly increasing) sensitivity to synthetic oxytocin during childbirth.

Mothering Behaviors

Endogenous oxytocin's role in mediating the initiation of maternal behavior has been demonstrated in numerous nonhuman species. Perinatal manipulation of the oxytocin system in animals provides strong evidence of subsequent dysfunctional maternal behaviors.⁴²⁻⁴⁶ For instance, in rats, oxytocin clearly mediates the initiation of maternal behavior.⁴⁴ In ewes, maternal acceptance of their own lamb occurs after identification, yet a central injection of synthetic oxytocin can promote maternal acceptance of alien lambs.⁴³ Optimal maternal behavior is blocked in ewes and heifers when central oxytocin is not released in physiologic birth due to regional anesthesia and subsequent lack of vagino-cervical stimulation.⁴⁶ In nonhuman primates, optimal maternal behavior can be altered by a central injection of synthetic oxytocin or by an oxytocin antagonist.^{42, 45}

One particular animal model has been useful in understanding the role of oxytocin in forming social bonds. The socially monogamous prairie vole forms pair bonds, an uncommon phenomenon among rodents of the opposite sex. It is postulated that the role of oxytocin buffers stress-reactivity as a function of social interaction and bonding.⁴ Research with this model points to the possibility of altering social behavior as a function of exposure

to synthetic oxytocin early in life. For example, in prairie vole pups, exposure to synthetic oxytocin on the first day of life had lasting and dose-dependent effects on the capacity to form pair bonds in later life. In this model, exposure to a low dose of synthetic oxytocin facilitated pair bonding later in that pup's life, while exposure to a high dose inhibited pair bond formation.⁴⁷ Exposure to an oxytocin antagonist in the same time period inhibited subsequent social behaviors including the typical willingness to care for unrelated infants (alloparenting), possibly mediated by increases in anxiety.⁴⁷ In addition, physiologic birth itself may be critical in the initiation of prairie vole maternal behavior. Female voles delivered by cesarean surgery have demonstrated infanticidal behavior; while females delivered vaginally (and that underwent a sham surgery following birth) did not.⁴⁸

A growing body of evidence suggests a link between oxytocin and optimal mothering behaviors in humans as well.^{49–53} Optimal mothering behaviors include affectionate touch, eye-to-eye contact, positive affect, and affectionate language that are characterized by sensitivity to infant cues and synchronous mother-infant interaction.⁵⁰ Synchronicity in mother-infant interaction has a strong effect on infant affective states. Numerous studies have found an association between atypical peripheral oxytocin levels and less optimal mothering behavior.⁵⁰ Genetic variation (i.e., risk alleles), and decreased central binding, of the OTR gene have also been associated with less optimal mothering behavior.^{49, 51, 52} A recent fMRI study of 15 parent-infant dyads found two distinct brain-behavior-oxytocin profiles in mothers displaying synchronous versus intrusive mothering behavior.⁵³ Mothers who displayed synchronicity in mother-infant interaction, had plasma oxytocin levels correlating with neural organization in reward-related motivational areas of the brain (left nucleus accumbens and right amygdala). In contrast, mothers who displayed intrusiveness in mother-infant interaction had no significant correlation between activation of neural reward areas and oxytocin levels. Additionally, the role of oxytocin in mothering behavior has been linked with the woman's affiliative experiences throughout her life (e.g., her own parents, partner and infant).⁵⁴ Again, it is unclear if any of these relationships are derived or influenced by the birth experience, or use of synthetic oxytocin. However, these findings do suggest that oxytocin plays a key role, beyond labor, in the transition to motherhood.

Lactation

The physiological transition to motherhood also includes establishing lactation. A few recent studies have examined lactation in the context of synthetic oxytocin and use of epidural anesthesia. For example, in Sweden 351 women who received an epidural were case-control matched with 351 women who did not receive an epidural.⁵⁵ Breastfeeding success was negatively associated with epidural use. Importantly, women who were augmented with synthetic oxytocin were three times less likely to initiate breastfeeding in the first four hours, and two times more likely to give artificial milk by the time of hospital discharge. Another small study ($n=20$) examined breastfeeding duration in relationship to intrapartum exposure to synthetic oxytocin during induction or augmentation of labor. All mothers had epidural anesthesia. Authors reported an inverse relationship between synthetic oxytocin dose and a shorter duration of exclusive breastfeeding by 3 months.⁵⁶

Consequences for the offspring

Evidence for long-term negative consequences for social behavior and the management of stressful experiences have repeatedly appeared in animal studies of offspring exposed to manipulations by oxytocin in early life. For example, work in piglets revealed that exposure to intranasal oxytocin in early life produced atypical, nonreciprocal social behavior and an altered capacity to respond to stressful experiences in later life.⁵⁷ Several studies in rodents similarly support the hypothesis that exposure to synthetic oxytocin, especially at high levels, during the perinatal period can have effects on the offspring.⁴

Studies of the long-term consequences of perinatal oxytocin exposure for children are less common. However, authors recently reported - based on a study in New York City of 3000 full term infants - that Pitocin[®]-treated infants showed an increase in multiple “adverse outcomes” including reductions in Apgar scores (indexed by increased pulse, breathing rate and “reflex irritability”) and increased admission to the NICU.⁵⁸ Increased admission to the NICU and other adverse effects, with an estimated 30% increase in measures of morbidity, also were seen in a 2012 study from Australia.⁵⁹ Neurodevelopmental risk for the offspring also was suggested by the finding that the occurrence of attention deficit disorders was twice as likely in children exposed to Pitocin[®] during birth.⁶⁰

Several studies have linked exposure to synthetic oxytocin to reductions in lactation, and diminished feeding-related behavior in the newborn.^{56, 61} These studies underscore the need for further research, especially taken in the context of a growing experimental literature in animals linking long-term behavioral outcomes to exposure to synthetic oxytocin in the perinatal period.

CONCLUSION

Oxytocin is a neuroendocrine hormone with complex actions throughout the body and effects vital to the mother-infant dyad and social well-being. Much remains to be understood about the role oxytocin plays in the transition to motherhood; however, emerging research in both animal and human models highlights the need for a deeper understanding of the role of physiologic birth in mother-infant biobehavioral outcomes important to the disciplines of midwifery and obstetrics.

Clearly, the role of oxytocin in the body extends far beyond uterine contractility to molecular cell systems that have potential long-term consequences. Downstream molecular effects of naturally-expressed oxytocin and synthetic oxytocin have not been investigated thoroughly in the context of human birth care. Midwifery and obstetric research should consider the oxytocin system as a whole, not just the immediate clinical result, when investigating the role of physiologic birth as well as birth interventions on biobehavioral outcomes in mothers and infants.

Research questions abound regarding the long-term implications of manipulating the oxytocin system during childbirth - an intricate transitional window of time for both mother and infant. One example may be early identification of women at-risk for postpartum mood disorders or lactation difficulties. Identifying at-risk women could potentially be informed by the interaction of OTR genotype, OTR epigenotype, and differential birth experiences impacting the regulation of endogenous oxytocin.

While many basic questions remain, we suggest that birth practitioners may benefit from an appreciation of the molecular, developmental and behavioral consequences of one of the most widely used drugs in obstetric practice. Given the lack of clarity and definitive research on the effects of oxytocin beyond labor, the dedication of health care professionals to minimal-interference in biologically-regulated and evolutionarily-conserved processes is warranted. There is great potential for interdisciplinary collaboration as the ubiquitous use of synthetic oxytocin in modern birth continues.

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Quick Points

- Downstream molecular effects of synthetic oxytocin have rarely been investigated in the context of human birth care.
- The role of natural oxytocin includes molecular pathways in the transition to motherhood, such as buffering stress reactivity, supporting positive mood and regulating healthy mothering behaviors.
- Given the action of natural oxytocin on various endocrine pathways, we anticipate that any effects of intrapartum synthetic oxytocin would be dose-dependent and influenced by individual context and maternal history.
- With the ubiquitous use of synthetic oxytocin in modern birth care, research questions abound regarding long-term implications of manipulating the oxytocin system during labor – a complex transitional window of development for both mother and infant.

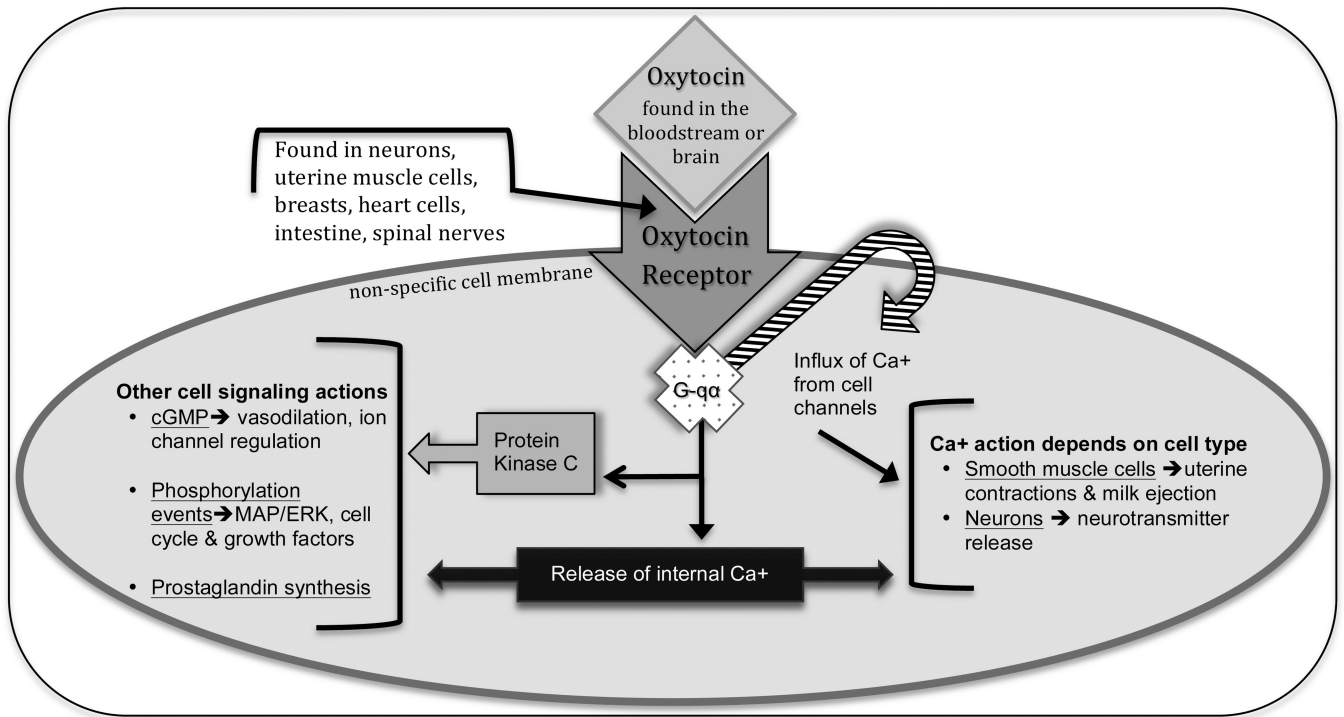


Figure 1.