Oxytocin Research
Overview: past, present & future discovery

November 14, 2019  -  Elise Erickson PhD, CNM
Disclosures

• No conflicts
Overview

• Briefly review physiology from the literature on oxytocin function broadly

• Oxytocin system in the birth process and pharmacologic implications for postpartum uterine function

• Oxytocin discovery on the horizon
Hypothalamic Neuroendocrine Peptide

Anterior (6 cell types)

Posterior (axon terminals)

Infundibulum

Hypophyseal Portal Circulation

Hypothalamic Neuroendocrine Peptide

Supraoptic nuclei

Paraventricular nuclei

Oxytocin/ Vasopressin

Anterior Pituitary

Posterior Pituitary

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Endogenous/Exogenous Oxytocin

Sir Henry Dale
- 1906: pituitary extracts
- 1911: clinical use

Vincent du Vigneaud
- 1953: Synthesized peptide sequence, structure
- 1955: Nobel prize
- First peptide ever synthesized

Present Use
- ~25% induced
- 30-57% (?) augmented
- AMTSL
- 2nd trimester termination/miscarriage management
Oxytocin Receptor (OXTR) Function

- Found in neurons, uterine muscle cells, breasts, heart cells, intestine, spinal nerves
- Oxytocin found in the bloodstream or brain

Other cell signaling actions:
- cGMP→ vasodilation, ion channel regulation
- Phosphorylation events→ MAP/ERK, cell cycle & growth factors
- Prostaglandin synthesis

G-qa

- Influx of Ca++ from cell channels

Protein Kinase C

- Release of internal Ca++

Ca++ action depends on cell type:
- Smooth muscle cells→ uterine contractions & milk ejection
- Neurons→ neurotransmitter release

Bell, Erickson, Carter (2014) Journal of Midwifery and Women’s Health
Where are oxytocin receptors found?

- Breast
- Myometrium
- Placenta
- Kidney/Adrenal
- Blood vessels
- Heart
- Platelets
- Bone
- Ovary
- Testicles
- Prostate
- Smooth muscle intestine
- Cancer cells
- Adipose cells


Peripheral oxytocin action

- Uterine muscle contraction
- Myoepithelium of breast—milk ejection
- Prostaglandin production (decidua-maternal side placenta)
- Decreased heart rate, blood pressure, temperature
- Decreased cortisol
- Suppression pro-inflammatory cytokines
- Increased glucose uptake & insulin secretion
- Cell growth (anti-proliferative)
- Inhibits growth of adipose cells

Central oxytocin action

- HPA axis (CRH->Cortisol)
- Dopaminergic pathways
- Serotonin neurons
- Vagus nerve: parasympathetic

OXT is a hypothalamic neuropeptide that functions like a neurotransmitter and a hormone throughout the body.
Regulation and Variation
How does endogenous oxytocin function vary between individuals?

And does it make a difference during the perinatal period?
Knockout Mice

Is oxytocin necessary for labor?


**Prostaglandin & Oxytocin Knockouts**

Days of gestation

<table>
<thead>
<tr>
<th>Period of gestation (day)</th>
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<tbody>
<tr>
<td>22</td>
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<td>21</td>
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**No OXTR** | **No OXT** |
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**Delivered Living Pups**

<table>
<thead>
<tr>
<th>Percentage of mice that delivered a living first pup</th>
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<tr>
<td>100</td>
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<td>50</td>
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<tr>
<th>WT</th>
<th>Ostr⁻⁻</th>
<th>Ox⁻⁻</th>
<th>Ptgfr⁻⁻⁻⁻</th>
<th>Ox⁻⁻⁻⁻</th>
<th>Ox⁻⁻⁻⁻⁻⁻</th>
<th>Ptgfr⁻⁻⁻⁻⁻⁻⁻⁻</th>
<th>Ptgfr⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻</th>
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4 cases
4 spontaneous labors at term
2 needed oxytocin augmentation in active phase
2 Cesareans, 1 instrument assisted birth
4 PPH (one delayed PPH)
4 no milk production
Labor & Genotype OXTR

Single Nucleotide Polymorphism (SNP): a single base pair variation in a genetic sequence that does not necessarily change the Amino Acid sequence of a protein, but may influence the overall efficiency of intracellular signaling.

Oxytocin in parturition:

OXT levels: Fetal blood > Maternal blood

Fig. 1. Phases of human parturition.

“...the need to ensure successful pregnancy likely produced a redundancy of pathways to ensure reliable uterine emptying and expulsion of the fetus.”
OXT / OXTR might not be a primary driver of the innate physiology of labor onset but is likely important during pushing and postpartum.
Pharmacokinetics of OXT

**Peptide**
- Half life
- *Degradation*

- Onset of action within 3 to 5 minutes
- Half-life studies: 3-6 minutes vs. 10 to 15 minutes (in blood, longer in CSF/brain)
- Steady state 30 to 60 minutes
- Degraded/inactivated by “oxytocinase”
  - Zinc-dependent aminopeptidase
  - PLAP (placental leucine aminopeptidase)
Oxytocin & Obesity

- Lower levels of oxytocin in circulation
- Lower levels post-menopause + obesity
  → Estrogen promotes upregulation of OXTR
- Less likely to start labor spontaneously
- Require higher doses during labor augmentation
- BMI >30, more likely to need to go over 20mu/min

Carlson (2015) Reproductive Biology & Endocrinology
Receptor Pharmacology

Receptor

↑ Upregulation (gestational age, hormone)
↓ Desensitization (binding)
↓ Degradation (via internalization)
↓ Down-regulation (mRNA)
Duration oxytocin

**Desensitization**
- OXT binding

**Duration of oxt**

**Maintenance dose mu/min**

**Downregulation**
- OXTR mRNA level

**HOURS IN LABOR**
- No labor
- 60x less
- Spontaneous labor
- Induced labor
- 300x less

CONTROL

Pretreatment 2 hours

Physiologic salt solution

Wait 6 hours

Increasing test dose concentration

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Low dose

10^{-8} M

Medium dose

10^{-8} M

High dose

10^{-9} to 10^{-12} M

Concentrations found in laboring women with augmentation.

10^{-8} M equivalent to a high dose protocols with induced labor.

Balki M et al. (2013) Anesthesiology.

Fig. 5. Representative data showing the contraction tracings. The effects of increasing concentrations of oxytocin (10^{-10} to 10^{-5} M) on the contractions of isolated myometrial strips pretreated with either PSS or 10^{-10}, 10^{-8}, or 10^{-5} M concentration of oxytocin for 2 h are shown. PSS = physiological salt solution.
OXT and OXTR function varies by gestational age, body habitus, and in the presence of an agonist.
• 4 previously published randomized controlled trials (published in the 1990s)

• \( n = 957 \) oxytocin vs. \( n = 1021 \) control group

• Effectiveness of prophylactic oxytocin for reducing PPH risk

• Women without synthetic oxytocin during labor

• Meta-analytic statistical test

Prophylactic oxytocin was not associated with lower rates of 1000mL blood loss, blood transfusion or need for more uterotonics meds.
Physiologic childbirth and active management of the third stage of labor: A latent class model of risk for postpartum hemorrhage

Elise N. Erickson PhD, CNM¹ | Christopher S. Lee PhD, RN, FAHA, FAAN, FHFS² | Emily Grose MN, CNM³ | Cathy Emeis PhD, CNM, FACNM¹

- OHSU Nurse-Midwifery Faculty Practice Repository
- n= 2,322 vaginal births (2012-2017)
- Childbirth Process Variables
- Role of Active Management of Third Stage Labor

**PHENOTYPES**

Dysfunctional/ prolonged
n = 819 (66% AMTSL, 33% did not)

- More PPH
- Less PPH w/ AMTSL (500mL)

Physiologic/ not prolonged
n = 1,028 (44% had AMTSL, 56% did not)

- Less PPH
- More PPH w/ AMTSL
- More retained placentas
Consortium for Safe Labor Dataset

National dataset, mid 2000s

Term Vaginal Births without major PPH risks

Excluded:
- Previa, Accreta, Abruption
- Thrombophilia/embolic disorders
- Major lacerations
- Prolonged 3rd stage-- >95\% tile (>15 minutes)
- Magnesium use in labor
- Chorioamnionitis
- Congenital anomalies

26,622 total sample size

Postpartum Hemorrhage: 1,007 (3.78%)
- EBL of 501mL or higher
- ICD9 Diagnosis Code

Current Study:
Oxytocin duration in labor and postpartum hemorrhage

Co-author:
Dr. Nicole Carlson, PhD, CNM
Emory University

*manuscript in preparation
PPH Frequency Following Vaginal Birth by Duration of Oxytocin Used in Labor. Consortium for Safe Labor Data

![Graph showing frequency of postpartum hemorrhage following vaginal birth by duration of oxytocin used in labor.](image)

**Spontaneous Labor**
- No oxytocin: 2.9%
- Up to 2 hours: 2.5%
- 2.1-4 hours: 4.6%
- 4.1-7 hours: 5.8%
- 7.1-12 hours: 6.1%
- Over 12 hours: 7.4%

- *n = 12,275, p < 0.001*

**Induction of Labor**
- No oxytocin: 3.8%
- Up to 2 hours: 3.5%
- 2.1-4 hours: 3.6%
- 4.1-7 hours: 3.7%

- *n = 14,347, p < 0.001*

*manuscript in preparation*
### Risk for Postpartum Hemorrhage by Duration of Oxytocin Use Augmented and Induced Labors (n = 2

<table>
<thead>
<tr>
<th>Oxytocin Duration</th>
<th>All Oxytocin Use</th>
<th>Augmentation Only</th>
<th>Induction Only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
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<td>aOR (95% CI)</td>
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<tr>
<td>&lt;=2 hours</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>&gt;2 hours to 4 hours</td>
<td>1.13 (0.89-1.42)</td>
<td>1.12 (0.87-1.43)</td>
<td>1.10 (0.73-1.63)</td>
</tr>
<tr>
<td>&gt;4 hours to 7 hours</td>
<td>1.47 (1.18-1.82)*</td>
<td>1.42 (1.13-1.79)*</td>
<td><strong>2.08 (1.45-2.98)</strong>*</td>
</tr>
<tr>
<td>&gt;7 hours to 12 hours</td>
<td>1.84 (1.47-2.30)*</td>
<td>1.72 (1.35-2.20)*</td>
<td><strong>2.29 (1.48-3.55)</strong>*</td>
</tr>
<tr>
<td>&gt;12 hours</td>
<td>2.74 (2.15-3.48)*</td>
<td>2.42 (1.81-3.22)*</td>
<td>2.49 (1.34-4.63)*</td>
</tr>
</tbody>
</table>

adjusted for parity, age, gestational age, level of weight gain, cervical dilation on admission

*manuscript in preparation
Postpartum Hemorrhage Associated with Term Vaginal Birth by Duration of Oxytocin (n = 26,662)

<table>
<thead>
<tr>
<th>Duration of Full Dilation</th>
<th>No Oxytocin</th>
<th>Oxytocin 4 hours or Less</th>
<th>Oxytocin &gt; 4 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 minutes or Less</td>
<td>2.7%</td>
<td>2.6%</td>
<td>3.8%</td>
</tr>
<tr>
<td>31-59 minutes</td>
<td>3.3%</td>
<td>2.5%</td>
<td>4.4%</td>
</tr>
<tr>
<td>60 to 179 minutes</td>
<td>4.3%</td>
<td>3.2%</td>
<td>6.6%</td>
</tr>
<tr>
<td>180+ minutes</td>
<td>4.8%</td>
<td>4.2%</td>
<td>9.1%</td>
</tr>
</tbody>
</table>

*p = 0.001, p = 0.006, p < 0.001, p = 0.03*
Other researchers:

**In vitro studies**
- Oxytocin pretreatment on myometrium for 2 hours results in diminished response even after removing oxytocin for up to 90 minutes (Balki, 2016)
- Oxytocin receptor internalization occurred after 15 minutes of exposure and recovery to cell membrane took up to 4 hours after exposure to be similar to baseline (Conti, 2009)

**In vivo studies**
- 490 women. Time from discontinuation of oxytocin during labor and Cesarean Delivery for dystocia was calculated (average of 99 minutes). Every 10 minute increase in recovery = 10 mL less blood loss.
  - However amount of oxytocin and duration of exposure was most related to need for PPH interventions. (Tran, 2017).
  - Women undergoing Cesarean required higher oxytocin dose infusions if oxytocin was previously administered (Lavoie, 2015).
Use of OXT during labor contributes to increased risk for postpartum hemorrhage, need for prophylaxis and further PPH treatment due to fewer available receptors.
Future of Oxytocin Research
Future Oxytocin Therapeutics

- **Carbetocin**: longer-lasting agonist (40 min half life)
  - Postpartum Hemorrhage?

- **Atosiban**: oxytocin receptor antagonist
  - Preterm labor?

- **Intranasal Oxytocin**: (central vs. peripheral debate)
  - Obesity/ blood glucose regulation
  - Cardiovascular protection during ischemia
  - Social behaviors/ mood symptoms
Oxytocin Receptor Expression In Pregnancy: When Does It Turn On?

- Dr. Jessica Reid - Family Planning Fellow
  - samples myometrium throughout late 2nd trimester to term
  - determine at what gestational age OXTR expression increases
  - inform clinical management of post-abortion hemorrhage

Higher DNAm = Lower OXTR
→ less uterine tone

- Postpartum Hemorrhage
- More exogenous oxytocin

Secondary outcomes
- Postpartum Mood
- Suboptimal Lactation
Summary

• OXT is a hypothalamic neuropeptide that functions like a neurotransmitter and a hormone.

• OXT / OXTR might not be a primary driver of the normal physiology of labor onset but is important during pushing and postpartum.

• OXT and OXTR function varies by gestational age, body habitus, and in the presence of an agonist (endogenous/exogenous).

• Use of OXT during labor contributes to increased risk for postpartum hemorrhage, need for prophylaxis and further PPH treatment due to fewer available receptors.

• Balancing goals of induced or speedy labor with need for functional oxytocin receptors after birth is something birth attendants should consider thoughtfully.
References

Thank You